

## Carbohydrates as Efficient Catalysts for the Hydration of $\alpha$ -Amino Nitriles

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## General Information

<sup>1</sup>H NMR experiments were recorded either on a Bruker AVANCE 300 MHz or 400 MHz instrument and calibrated to the residual solvent peak (e.g. CHCl<sub>3</sub> peak at 7.26 ppm). <sup>13</sup>C NMR spectra were recorded at 75 MHz or 100 MHz and calibrated to the solvent peak (e.g. CDCl<sub>3</sub> at 77.23 ppm). The chemical shifts are reported in parts per million (ppm) relative to the corresponding protio-solvent signal. High-resolution mass spectra were obtained by EI on a Kratos Concept IIF or ESI on micromass Q-TOF. Infrared analysis was performed on an ABB Bomem Arid-Zone and the spectra were obtained as neat films on a sodium chloride window. Column chromatography was performed using silica gel, 40 microns flash silica. Thin layer chromatography was performed on silica gel (Silica Gel 60 F254) glass plates/aluminum back plates and the compounds were visualized by UV, 0.5% KMnO<sub>4</sub> in 0.1 M aqueous NaOH solution and/or 5% ninhydrin in EtOH. Unless otherwise noted, all reagents were used as is from commercial sources.

The commercially available HCl salts of  $\alpha$ -aminonitriles **1c** and **3n** were used directly in the procedures below (with an extra equivalent of NaOH for deprotonation in situ) and unless detailed below known  $\alpha$ -aminonitriles were synthesized according to literature procedures. Formaldehyde solution: a commercially available solution from Sigma-Aldrich was used (37 wt% in water).<sup>1</sup> Sodium hydroxide was used as a 5 M stock solution in water. The aldehydes and ketones used as catalysts were commercially available from Sigma-Aldrich.

## Catalyst screening

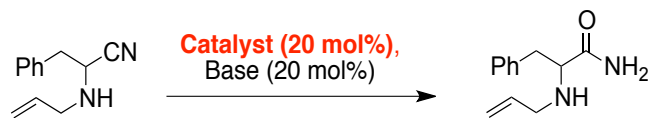
### *Procedure for the hydration of primary $\alpha$ -aminonitrile **1a***

2-Amino-4-methylthiobutyronitrile (0.075 g, 0.50 mmol) was taken up in D<sub>2</sub>O (0.50 mL). NaOH (20 mL, 0.10 mmol) was added followed by the aldehyde (0.10 mmol). The mixture was allowed to stir for desired time at rt under argon. The reaction mixture was then diluted with DMSO-d<sub>6</sub> (0.50 mL). The reaction mixture was then evaporated under reduced pressure to remove majority of D<sub>2</sub>O. A known amount of 1,3,5-trimethoxybenzene was added. The reaction was analyzed by <sup>1</sup>H NMR and the yield was calculated using the 1,3,5-trimethoxybenzene as an internal standard.

### *Procedure for the hydration of secondary $\alpha$ -aminonitrile **1b***

2-(*N*-Allylamino)-3-phenylpropionitrile (0.054 g, 0.39 mmol) was taken up in H<sub>2</sub>O. NaOH (16 mL, 0.08 mmol) was added followed by the aldehyde (0.08 mmol). The mixture was allowed to stir for desired time at rt under argon. The reaction mixture was then diluted with EtOAc (5 mL) and H<sub>2</sub>O (1 mL). The aqueous and organic layers were separated. The aqueous layer was extracted with EtOAc (4 x 5 mL). The combined organic layers were dried and concentrated. The crude was weighed and a known amount of 1,3,5-trimethoxybenzene (0.017 g, 0.10 mmol) was added. The resulting mixture was then dissolved in CDCl<sub>3</sub>. The reaction was analyzed by <sup>1</sup>H NMR and the yield was calculated using the 1,3,5-trimethoxybenzene as an internal standard. Yields and percentage conversions for different aldehydes are given in the table below (Table 1).

**Table S1. Carbonyl catalyst screening for hydration of *N*-allyl- $\alpha$ -aminonitrile 1b**



Entry	Catalyst	Reaction time	Starting material (%)	Product (%)
1	No Catalyst	24 h	-	15
2		5 min	60	39
		30 min	12	72
		2 h	0	86
3		5 min	90	4
		30 min	83	7
		2 h	79	8
		12 h	71	9
4		1.5 h	0	69
5		12 h	No reaction	No reaction
6		12 h	No reaction	No reaction
7		2.5 h	0	52
8		12 h	No reaction	No reaction
9		12 h	No reaction	No reaction

## Survey of different bases

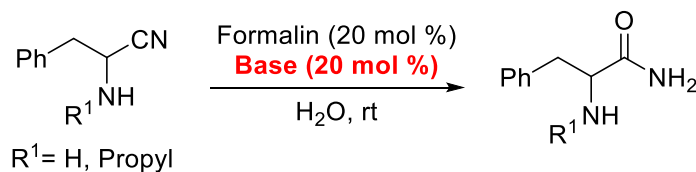
### *Procedure for the hydration of primary $\alpha$ -aminonitrile **1v***

2-Amino-3-phenylpropanenitrile (0.059 g, 0.40 mmol) was taken up in D<sub>2</sub>O (0.50 mL). The base (0.080 mmol) was added followed by formaldehyde (6.0  $\mu$ L, 0.080 mmol). The mixture was allowed to stir for 3 hours at rt under argon. The reaction mixture was then diluted with MeOD-d<sub>4</sub> (0.50 mL) followed by the addition of a known amount of 1,2-dimethoxyethane. The reaction was analyzed by <sup>1</sup>H NMR and the yield was calculated using the 1,2-dimethoxyethane as an internal standard. Yields and percentage conversions for different bases are given in the table below (Table S2).

### *Procedure for the hydration of secondary $\alpha$ -aminonitrile **1w***

3-Phenyl-2-(propylamino)propanenitrile (0.075 g, 0.40 mmol) was taken up in H<sub>2</sub>O (0.4 mL). The base (0.080 mmol) was added followed by the formaldehyde (6.0  $\mu$ L, 0.08 mmol). The mixture was allowed to stir for 3 hours at rt under argon. The reaction mixture was then diluted with MeOD-d<sub>4</sub> (0.50 mL) followed by the addition of a known amount of 1,2-dimethoxyethane. The reaction was analyzed by <sup>1</sup>H NMR and the yield was calculated using the 1,2-dimethoxyethane as an internal standard. Yields and percentage conversions for different bases are given in the table below (Table S2).

**Table S2. Survey of different bases for the hydration of  $\alpha$ -aminonitriles**



<b>R<sup>1</sup> = H</b>		<b>R<sup>1</sup> = Propyl</b>	
<b>Base</b>	<b>Yield (%)</b>	<b>Base</b>	<b>Yield (%)</b>
NaOH	63	NaOH	96
LiOH	60	LiOH	93
KOH	63	KOH	99
CsOH	69	CsOH	97

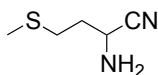
## Synthesis of primary $\alpha$ -aminonitriles

### General procedure for the Synthesis of primary $\alpha$ -aminonitriles (Procedure A)

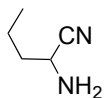
NaCN was taken up in H<sub>2</sub>O (11.0 mL) and stirred for 5 min at rt. NH<sub>4</sub>Cl (1.10 mmol) was then added. The reaction was stirred until almost all of the NH<sub>4</sub>Cl (1.00 mmol) was dissolved. The aldehyde (1.00 mmol) dissolved in MeOH (11.0 mL) was then added to the reaction mixture. This was stirred vigorously for 12 h at rt. After completion, as indicated by TLC (petroleum ether/EtOAc, 85:15), the reaction mixture was diluted with EtOAc (20 mL). The aqueous and organic layers were separated and the aqueous layer was extracted with EtOAc (25 mL x 4). The organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified using flash column chromatography (petroleum ether/EtOAc/aq NH<sub>4</sub>OH).

### General procedure for the synthesis of primary $\alpha$ -aminonitriles (Procedure B)

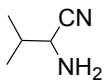
$\alpha$ -Aminonitriles were synthesized by subjecting the corresponding aldehyde or ketone to Strecker conditions according to the procedure by Garst.<sup>2</sup> KCN (1.10 mmol) was taken up in H<sub>2</sub>O (0.30 mL). NH<sub>4</sub>Cl (1.20 mmol) was added and the solution was stirred until it was homogenous. A solution of aldehyde (1.00 mmol) in MeOH (0.30 mL) was then added drop-wise over a period of one hour. The reaction mixture was then heated to 60 °C until completion by TLC. It was then diluted with CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and H<sub>2</sub>O (5 mL). The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL x 3) and the combined organic extracts were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified using flash column chromatography (petroleum ether/EtOAc/aq NH<sub>4</sub>OH).



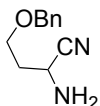
**2-Amino-4-methylthiobutyronitrile (1a).** Synthesized according to Procedure B with 3-methylthiopropanaldehyde (8.85 g, 85.0 mmol). Purification by silica gel chromatography (petroleum ether/EtOAc/aq NH<sub>4</sub>OH, 49:50:1, TLC R<sub>f</sub> = 0.35) gave a red-orange oil (2.87 g, 26%): <sup>1</sup>H NMR (300 MHz, D<sub>2</sub>O) δ 3.74 (t, *J* = 7.2 Hz, 1H), 2.59-2.44 (m, 2H), 1.95 (s, 3H), 1.88-1.81 (m, 2H), 1.69 (br s, 2H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 121.8, 41.6, 33.9, 29.4, 15.0. Spectral data was consistent with literature.<sup>3</sup>



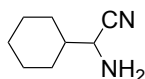
**2-Aminopentanenitrile (1d).** Synthesized according to Procedure A with butyraldehyde (2.00 g, 28.0 mmol). Purification by silica gel chromatography (petroleum ether/EtOAc/aq NH<sub>4</sub>OH, 49:50:1, TLC R<sub>f</sub> = 0.30) gave an orange-yellow oil (0.96 g, 35%): <sup>1</sup>H NMR (300 MHz, D<sub>2</sub>O) δ 3.66 (t, *J* = 7.1 Hz, 1H), 2.37 (br s, 2H), 1.71-1.65 (m, 2H), 1.54-1.43 (m, 2H), 1.13 (br m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 122.3, 43.2, 37.3, 18.8, 13.5. Spectral data was consistent with literature.<sup>4</sup>



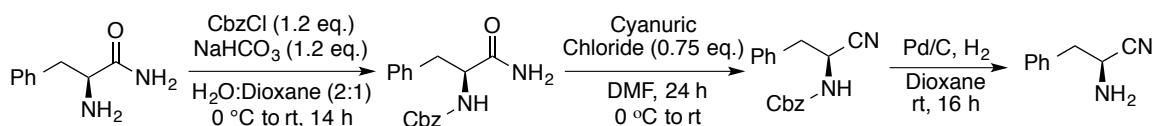
**2-Amino-3-methylbutyronitrile (1e).** Synthesized according to procedure B with isobutyraldehyde (2.00 g, 27.3 mmol). Purification by silica gel chromatography (petroleum ether/EtOAc/aq NH<sub>4</sub>OH, 49:50:1, TLC R<sub>f</sub> = 0.25) gave a yellow oil (1.28 g, 48%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 3.55 (d, *J* = 5.6 Hz, 1H), 1.96 (m, 1H), 1.77 (br s, 2H), 1.10 (d, *J* = 2.5 Hz, 3H), 1.08 (d, *J* = 2.5 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 121.1, 49.6, 32.7, 18.6, 17.4. Spectral data was consistent with literature.<sup>5</sup>



**2-Amino-4-(benzyloxy)butyronitrile (1f).** Synthesized according to Procedure A with 3-(benzyloxy)propionaldehyde (1.79 g, 10.9 mmol).<sup>6</sup> Purification by silica gel chromatography (CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH/NH<sub>4</sub>OH, 94:5:1, TLC *R<sub>f</sub>* = 0.57) gave 2-amino-4-(benzyloxy)butyronitrile (**1f**) as a clear yellow oil (1.86 g, 90%): IR (film): 3393, 3321, 3096, 3062, 3023, 2960, 2937, 2868, 2800, 2226, 1603, 1496, 1451, 1360 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.28-7.45 (m, 5H), 4.54 (s, 2H), 3.97 (t, *J* = 6.9 Hz, 1H), 3.71-3.79 (m, 1H), 3.63-3.71 (m, 1H), 2.04 (m, 2H), 1.75 (br s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 137.7, 128.3, 127.6, 127.5, 121.8, 73.0, 65.8, 40.9, 34.9; HRMS (EI): Exact mass calculated for C<sub>10</sub>H<sub>14</sub>NO [M-CN]<sup>+</sup>, 164.1075; Found: 164.1090.



**2-Amino-2-cyclohexylacetone nitrile (1k).** Synthesized according to Procedure A using cyclohexylcarboxaldehyde (1.50 g, 9.13 mmol). Purification by flash column chromatography on silica gel (hexanes/EtOAc, 80:20, TLC *R<sub>f</sub>* = 0.20) provided a white solid (0.68 g, 54%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 3.53 (d, *J* = 5.9 Hz, 1H), 1.95-1.54 (m, 8H), 1.36-1.07 (m, 5H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 121.1, 48.7, 41.7, 29.0, 27.9, 25.6, 25.3, 25.3. Spectral data was consistent with literature.<sup>7</sup>



**(L)-2-Amino-3-phenylpropanenitrile (1v).** Enantiopure α-aminonitrile starting material was obtained using a modified procedure from Rodriguez.<sup>8</sup> (*L*)-2-amino-3-phenylpropanamide HCl (1.0 g, 5.0 mmol) and sodium bicarbonate (0.67 g, 11.0 mmol)

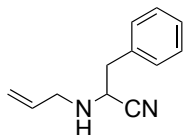


were dissolved in a 2:1 mixture of H<sub>2</sub>O/dioxane (13 mL/7 mL). The mixture was cooled to 0 °C and benzyl chloroformate (0.86 mL, 6.0 mmol) was added to the solution dropwise. The mixture was warmed to rt and stirred for 14 h. The mixture was diluted with EtOAc (40 mL) and washed with water (20 mL) and brine (2 x 20 mL). The organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give the crude product as a white solid. Purification by recrystallization in MeOH provided (*L*)-benzyl(1-amino-1-oxo-3-phenylpropane-2-yl)carbamate as a white solid (1.03 g, 69%): <sup>1</sup>H-NMR (300 MHz; CDCl<sub>3</sub>): δ 7.36-7.18 (m, 10H), 5.69 (s, 1H), 5.41 (s, 1H), 5.36 (s, 1H), 5.07 (s, 2H), 4.45-4.37 (m, 1H), 3.10-3.04 (m, 2H). Spectral data was consistent with the literature.<sup>9</sup> (*L*)-Benzyl(1-amino-1-oxo-3-phenylpropane-2-yl)carbamate (1.03 g, 3.5 mmol) was dissolved in DMF (3.5 mL) and cooled to 0 °C for the addition of 2,4,6-trichloro-1,3,5-triazine (0.48 g, 2.6 mmol). The mixture was warmed to rt and stirred for 24 h. The mixture was subsequently diluted with EtOAc (30 mL) and washed with a 1:1 water: brine mixture (3 x 20 mL). The organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give the crude product as a colourless oil. Purification by column chromatography (petroleum ether/EtOAc, 80:20, TLC R<sub>f</sub> = 0.23) provided (*L*)-benzyl(1-cyano-2-phenylethyl)carbamate as a white solid (0.53 g, 54%): <sup>1</sup>H-NMR (400 MHz; CDCl<sub>3</sub>): δ 7.37-7.23 (m, 10H), 5.23-5.21 (m, 1H), 5.10 (s, 2H), 4.87-4.86 (m, 1H), 3.11-3.00 (m, 2H). Spectral data was consistent with the literature.<sup>10</sup> (*L*)-Benzyl(1-cyano-2-phenylethyl)carbamate (0.53 g, 1.8 mmol) was then suspended in dioxane (13.0 mL). 10 % Palladium on carbon (0.15 g) was added to the solution. The solution was then purged with hydrogen gas for 5 minutes and stirred under a hydrogen atmosphere for 16 h. The solution was then filtered through celite and washed with EtOAc (100 mL) and subsequently concentrated under reduced pressure providing pure (*L*)-2-Amino-3-phenylpropanenitrile as a white solid (0.260 g, 99%): (Petroleum ether/EtOAc/aq NH<sub>4</sub>OH, 50/49/1, TLC R<sub>f</sub> = 0.30) <sup>1</sup>H-NMR (400 MHz; CDCl<sub>3</sub>): δ 7.36-7.27 (m, 5H), 3.92 (t, *J* = 6.5 Hz, 1H), 3.01 (dd, *J* = 6.5, 1.4 Hz, 2H), 1.66 (s, 2H). Spectral data was consistent with the literature.<sup>5</sup>

## Synthesis of secondary $\alpha$ -aminonitriles

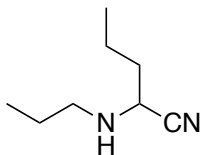
### General procedure for the synthesis of secondary $\alpha$ -aminonitriles

Aldehyde (1.0 mmol) and amine (1.0 mmol) were taken up in H<sub>2</sub>O (5.0 mL). This was stirred vigorously for 10 min at rt. After 10 min, additional H<sub>2</sub>O (4.0 mL) was added followed by acetonecyanohydrin (1.0 mmol). The reaction mixture was stirred at rt for 8 to 10 h. After completion, as indicated by TLC (petroleum ether/EtOAc, 85:15), the reaction mixture was diluted with EtOAc (10 mL). Aqueous and organic layers were separated and the aqueous layer was extracted with EtOAc (15 mL x 4). The organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified using flash column chromatography (petroleum ether/EtOAc).

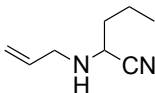


**2-(*N*-Allylamino)-3-phenylpropanenitrile (1b).** NaCN (3.20 g, 65.7 mmol) was dissolved in H<sub>2</sub>O (26.0 mL). Allylamine (3.00 g, 52.5 mmol) was then added and reaction mixture was stirred for 5 to 10 min at rt. Phenylacetaldehyde (6.30 g, 52.5 mmol) dissolved in MeOH (26.0 mL) was then added dropwise to the reaction mixture. The resulting mixture was stirred at rt for 10 to 12 h. After completion of the reaction, as indicated by TLC (petroleum ether/EtOAc, 85:15), the reaction mixture was diluted with EtOAc (30 mL) and H<sub>2</sub>O (10 mL). Aqueous and organic layers were separated. The aqueous layer was extracted with EtOAc (25 mL x 4). The organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give the crude product as an orange-red oil. Purification by column chromatography on silica gel (petroleum ether/EtOAc, 85:15 to petroleum ether/EtOAc, 80:20, TLC R<sub>f</sub> = 0.3) afforded 2-(*N*-allylamino)-3-phenylpropanenitrile (**1b**) as a pale orange oil (3.98 g, 40%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.39-7.27 (m, 5H), 5.83 (dddd, *J* = 17.0, 10.2, 6.6, 5.5 Hz, 1H), 5.25 (dddd, *J* = 17.2, 1.6, 1.6, 1.6 Hz, 1H), 5.16 (dddd, *J* = 10.2, 1.4, 1.4, 1.4 Hz, 1H), 3.79 (dd, *J* = 7.3, 5.6 Hz, 1H),

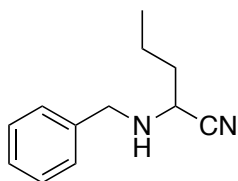
3.53 (ddd,  $J = 5.5, 1.5, 1.5$  Hz, 1H), 3.28 (ddd,  $J = 6.6, 1.3, 1.3$  Hz, 1H), 3.13-2.98 (m, 2H), 1.38 (br s, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  135.2, 134.9, 129.6, 128.9, 127.7, 119.6, 117.7, 50.9, 50.2, 39.5. Spectral data was consistent with literature.<sup>11</sup>



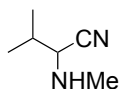
**2-(*N*-Propylamino)pentanenitrile (1g).** The general procedure for the synthesis of secondary  $\alpha$ -aminonitriles was followed with propylamine (2.00 g, 33.8 mmol), acetone cyanohydrin (2.88 g, 33.8 mmol), and butyraldehyde (2.44 g, 33.8 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc, 85:15 to petroleum ether/EtOAc, 80:20, TLC  $R_f = 0.25$ ) afforded 2-(*N*-propylamino)pentanenitrile (**1g**) as a colorless oil (3.23 g, 68%): IR (film): 2961, 2876, 2226, 1464, 1087  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  3.47 (t,  $J = 7.1$  Hz, 1H), 2.77 (m, 1H), 2.52 (m, 1H), 1.67 (m, 2H), 1.55-1.37 (m, 4H), 1.18 (br s, 1H), 0.91 (t,  $J = 7.1$  Hz, 3H), 0.89 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  120.5, 50.5, 49.6, 35.6, 22.9, 19.0, 13.5, 11.6; HRMS (EI): Exact mass calcd for  $\text{C}_5\text{H}_9\text{N}_2$  [ $\text{M} - \text{CH}_2\text{CH}_2\text{CH}_3$ ] $^+$ , 97.0766; Found 97.0758.



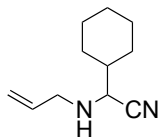
**2-(*N*-Allylamino)pentanenitrile (1h).** The general procedure for the synthesis of *N*-substituted- $\alpha$ -aminonitriles was followed using allylamine (2.00 g, 35.0 mmol), acetonecyanohydrin (2.98 g, 35.0 mmol) and butyraldehyde (2.53 g, 35.0 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc, 85:15 to petroleum ether/EtOAc, 80:20, TLC  $R_f = 0.25$ ) afforded 2-(*N*-allylamino)pentanenitrile (**1h**) as a clear oil (2.88 g, 60%):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  5.83 (m, 1H), 5.25 (m, 1H), 5.15 (m, 1H), 3.55-3.47 (m, 2H), 3.27 (m, 1H), 1.77-1.69 (m, 2H), 1.61-1.43 (m, 2H), 1.39 (br s, 1H), 0.95 (t,  $J = 7.3$  Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  135.1, 120.4, 117.7, 50.4, 49.6, 35.6, 19.1, 13.6. Spectral data was consistent with literature.<sup>12</sup>



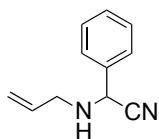
**2-(*N*-Benzylamino)pentanenitrile (1i).** The general procedure for the synthesis of secondary  $\alpha$ -aminonitriles was followed with benzylamine (0.210 g, 2.00 mmol), acetonecyanohydrin (0.170 g, 2.00 mmol) and butyraldehyde (0.140 g, 2.00 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc, 85:15 to petroleum ether/EtOAc, 80:20, TLC  $R_f = 0.25$ ) afforded 2-(*N*-benzylamino)pentanenitrile (**1i**) as a colorless oil (0.310 g, 82%):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.36-7.26 (m, 5H), 4.02 (d,  $J = 12.9$  Hz, 1H), 3.78 (d,  $J = 12.9$  Hz, 1H), 3.45 (m, 1H), 2.16 (br s, 1H), 1.71 (m, 2H), 1.55-1.48 (m, 2H), 0.94 (t,  $J = 7.3$  Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  120.2, 52.3, 35.3, 34.2, 19.1, 13.6. Spectral data was consistent with literature.<sup>13</sup>



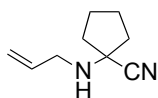
**2-*N*-Methylamino-3-methylbutyronitrile (1j).** Synthesized according to procedure B with isobutyraldehyde (2.78 g, 38.5 mmol, 3.50 mL) and *N*-methylamine (40% w/w sol in  $\text{H}_2\text{O}$ , 38.5 mmol, 3.50 mL). Purification by silica gel chromatography (petroleum ether/EtOAc/aq  $\text{NH}_4\text{OH}$ , 49:50:1, TLC  $R_f = 0.25$ ) gave a yellow oil (2.20 g, 53%):  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.24 (d,  $J = 6.0$  Hz, 1H), 2.54 (s, 3H), 1.98 (m, 1H), 1.07 (d,  $J = 2.9$  Hz, 3H), 1.05 (d,  $J = 2.9$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  119.2, 59.4, 34.6, 31.3, 19.2, 18.2. Spectral data was consistent with literature.<sup>14</sup>



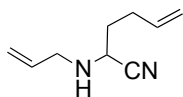
**2-(*N*-Allylamino)-2-cyclohexylacetonitrile (11).** The general procedure for the synthesis of *N*-allyl- $\alpha$ -aminonitriles was followed with allylamine (1.00 g, 17.8 mmol), acetonecyanohydrin (1.51 g, 17.8 mmol) and cyclohexylcarboxaldehyde (2.0 g, 17.8 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc, 85:15 to petroleum ether/EtOAc, 80:20, TLC  $R_f$  = 0.25) afforded 2-(*N*-allylamino)-2-cyclohexylacetonitrile (**11**) as a colorless oil (1.92 g, 60%): IR (film): 2930, 2854, 2224, 1451, 1097  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  5.82 (m, 1H), 5.25 (dddd,  $J$  = 17.2, 1.5, 1.5, 1.5 Hz, 1H), 5.14 (dddd,  $J$  = 10.2, 1.2, 1.2, 1.2 Hz, 1H), 3.50 (dddd,  $J$  = 13.7, 2.7, 1.4, 1.4 Hz, 1H), 3.33 (d,  $J$  = 6.1 Hz, 1H), 3.25 (dddd,  $J$  = 13.7, 2.2, 1.1, 1.1 Hz, 1H), 1.85-1.75 (m, 3H + NH), 1.69-1.60 (m, 2H), 1.32-1.06 (m, 6H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  135.3, 119.7, 117.6, 55.6, 50.6, 40.9, 29.9, 28.9, 26.2, 25.9, 25.8; HRMS (EI): Exact mass calcd for  $\text{C}_8\text{H}_{13}\text{N}_2$  [ $\text{M} - \text{CH}_2\text{CHCH}_2$ ] $^+$ , 137.1079; Found 137.1066.



**2-(*N*-Allylamino)-2-phenylacetonitrile (1n).** The general procedure for the synthesis of *N*-allyl- $\alpha$ -aminonitriles was followed with allylamine (1.10 g, 18.8 mmol), acetonecyanohydrin (1.60 g, 18.8 mmol) and benzaldehyde (2.00 g, 18.8 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc, 85:15 to petroleum ether/EtOAc, 80:20, TLC  $R_f$  = 0.25) afforded 2-(*N*-allylamino)-2-phenylacetonitrile as (**1n**) pale yellow oil (2.43 g, 75%):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.55-7.52 (m, 2H), 7.45-7.37 (m, 3H), 5.90 (dddd,  $J$  = 17.0, 10.2, 6.5, 5.6 Hz, 1H), 5.32 (dddd,  $J$  = 17.2, 1.6, 1.6, 1.6 Hz, 1H), 5.21 (dddd,  $J$  = 10.2, 1.3, 1.3, 1.3 Hz, 1H), 4.80 (s, 1H), 3.56-3.38 (m, 2H), 1.64 (br s, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  135.0, 135.0, 129.3, 129.2, 127.5, 119.0, 118.1, 53.7, 50.1. Spectral data was consistent with literature.<sup>15</sup>

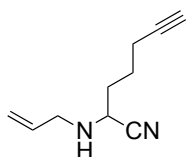


**1-(*N*-Allylamino)-1-cyclopentanecarbonitrile (1o).** The general procedure for the synthesis of *N*-allyl- $\alpha$ -aminonitriles was followed with allylamine (1.36 g, 23.8 mmol), acetonecyanohydrin (2.02 g, 23.8 mmol) and cyclopentanone (2.00 g, 23.8 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc, 85:15 to petroleum ether/EtOAc, 80:20, TLC  $R_f$  = 0.3) afforded 1-(*N*-allylamino)-1-cyclopentanecarbonitrile (**1o**) as a colorless oil (1.70 g, 48%): IR (film): 3321, 2971, 2221, 1206  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  5.81 (m, 1H), 5.15 (dddd,  $J$  = 17.1, 1.5, 1.5, 1.5 Hz, 1H), 5.02 (dddd,  $J$  = 10.2, 1.4, 1.4, 1.4 Hz, 1H), 3.26 (m, 1H), 3.24 (m, 1H), 2.06-1.96 (m, 2H), 1.76-1.68 (m, 6H), 1.42 (br s, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  135.6, 122.7, 116.3, 60.9, 48.3, 38.8, 23.4; HRMS (EI): Exact mass calcd for  $\text{C}_{19}\text{H}_{13}\text{N}_2$  [ $\text{M}-\text{H}^+$ ], 149.1079; Found 149.1072.

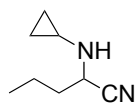


**2-(*N*-Allylamino)-5-hexanenitrile (1p).** A solution of 4-pentenal<sup>16</sup> (0.528 g, 6.28 mmol) in  $\text{CH}_2\text{Cl}_2$  (6.0 mL) and allylamine (0.538 g, 9.42 mmol) were taken up in  $\text{H}_2\text{O}$  (31 mL) and stirred vigorously for 10 min at rt. After 10 min, additional  $\text{H}_2\text{O}$  (25 mL) was added followed by acetonecyanohydrin (0.558 g, 6.91 mmol). The reaction mixture was stirred at rt for 15 hours. After completion, as indicated by TLC (Hexanes/EtOAc, 80:20), the reaction mixture was diluted with  $\text{Et}_2\text{O}$  (30 mL). The aqueous and organic layers were separated and the aqueous layer was extracted with  $\text{Et}_2\text{O}$  (30 mL x 3). The organic layers were combined, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified using flash column chromatography (Hexanes/EtOAc, 90:10; TLC  $R_f$  = 0.26 in Hexanes/EtOAc, 80:20) to provide 2-(*N*-allylamino)-5-hexanenitrile (**1p**) as colorless oil (0.353 g, 38 %); IR (neat film, NaCl): 3325, 3079, 3006, 2984, 2930, 2847, 2227, 1853, 1643, 1455, 1418, 1352, 1318  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.73-5.92

(m, 2H), 5.29 (dq,  $J = 17.2, 1.6$  Hz, 1H), 5.15-5.20 (m, 1H), 5.11 (dq,  $J = 17.2, 1.6$  Hz, 1H), 5.06 (dq,  $J = 10.2, 1.3$  Hz, 1H), 3.49-3.61 (m, 2H), 3.26-3.34 (m, 1H), 2.21-2.38 (m, 2H), 1.87 (q,  $J = 7.5$  Hz, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  136.2, 134.9, 120.0, 117.6, 116.5, 50.2, 49.0, 32.6, 29.7; HRMS (EI): Exact mass calculated for  $\text{C}_5\text{H}_7\text{N}_2$   $[\text{M}-\text{C}_4\text{H}_7]^+$ , 95.0609; Found 95.0620, exact mass calculated for  $\text{C}_4\text{H}_7$   $[\text{M}-\text{C}_5\text{H}_7\text{N}_2]^+$ , 55.0548; Found 55.0528.

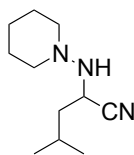


**2-(*N*-Allylamino)hept-6-ynonitrile (1q).** The general procedure for the synthesis of *N*-allyl- $\alpha$ -aminonitriles was followed with allylamine (0.30 g, 5.2 mmol), acetonecyanohydrin (0.44 g, 5.2 mmol) and 5-hexynal (0.50 g, 5.2 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc, 85:15 to petroleum ether/EtOAc, 80:20, TLC  $R_f = 0.25$ ) afforded 2-(*N*-allylamino)hept-6-ynonitrile (**1q**) as a colorless oil (0.35 g, 42%): IR (neat film, NaCl) 3081, 2936, 2871, 2228, 1110  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  5.83 (m, 1H), 5.26 (dddd,  $J = 17.1, 1.6, 1.6, 1.6$  Hz, 1H), 5.15 (dddd,  $J = 10.2, 1.3, 1.3, 1.3$  Hz, 1H), 3.56 (t,  $J = 7.0$  Hz, 1H), 3.51 (dddd,  $J = 13.7, 3.0, 1.5, 1.5$  Hz, 1H), 3.28 (dddd,  $J = 13.7, 2.6, 1.3, 1.3$  Hz, 1H), 2.28-2.22 (m, 2H), 1.97 (t,  $J = 2.6$  Hz, 1H), 1.93-1.85 (m, 2H), 1.77-1.67 (m, 2H), 1.31 (br s, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  135.0, 120.1, 117.8, 83.2, 69.5, 50.3, 49.4, 32.5, 24.6, 18.0; HRMS (EI): Exact mass calcd for  $\text{C}_{10}\text{H}_{13}\text{N}_2$   $[\text{M} - \text{H}]^+$ ; 161.1079, Found 161.1102.

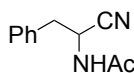


***N*-Cyclopropyl-2-aminopentanenitrile (1r).** Butyraldehyde (1.26 g, 17.5 mmol) and cyclopropylamine (1.00 g, 17.5 mmol) was taken up in  $\text{H}_2\text{O}$  (88.0 mL). This was stirred vigorously for 10 min at rt. After 10 min, additional  $\text{H}_2\text{O}$  (70.0 mL) was added followed by acetonecyanohydrin (1.49 g, 17.5 mmol). The reaction mixture was stirred at rt for 8

to 10 h. After completion, as indicated by TLC (petroleum ether/EtOAc, 85:15), the reaction mixture was diluted with EtOAc (50 mL). The aqueous and organic layers were separated and the aqueous layer was extracted with EtOAc (25 mL x 4). The organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by flash column chromatography (petroleum ether/EtOAc, 80:20, TLC R<sub>f</sub> = 0.30) gave *N*-cyclopropyl-2-aminopentanenitrile (**1r**) as clear oil (1.42 g, 59%): IR (film): 3094, 2962, 2873, 2228, 1425, 1218 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 3.51 (t, *J* = 7.1 Hz, 1H), 2.31 (m, 1H), 1.85 (br s, 1H), 1.67-1.59 (m, 2H), 1.50-1.37 (m, 2H), 0.88 (t, *J* = 7.3 Hz, 3H), 0.54-0.37 (m, 3H), 0.26-0.18 (m, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 120.8, 50.4, 35.4, 28.5, 18.9, 13.4, 7.1, 5.8; HRMS (EI): Exact mass calcd for C<sub>8</sub>H<sub>14</sub>N<sub>2</sub> [M]<sup>+</sup>, 138.1157; Found 138.1428.



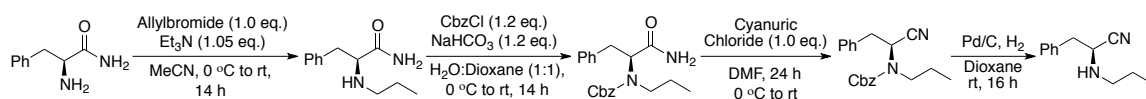
**2-(Piperidin-1-ylamino)-4-methylvaleronitrile (3s).** Prepared as described in literature.<sup>17</sup>



**2-(*N*-Acetylamino)-3-phenylpropionitrile (1t).** 2-Amino-3-phenylpropionitrile (0.29 g, 2.0 mmol) was dissolved in THF (4 mL) and cooled down to 0 °C. Et<sub>3</sub>N (0.40 g, 4.0 mmol, 0.55 mL) was added to the solution. Acetic anhydride (4.0 mmol, 0.38 mL) was then added dropwise to the solution. The reaction was warmed up to rt slowly, and then stirred at rt for 1-2 h (monitored by TLC). The reaction mixture was then diluted with EtOAc (10 mL) and H<sub>2</sub>O (10 mL). The aqueous and organic layers were separated. The aqueous layer was extracted with EtOAc (3 x 15 mL). The organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by silica gel chromatography (petroleum ether/EtOAc/aq NH<sub>4</sub>OH, 49:50:1, TLC R<sub>f</sub> = 0.20) gave a low melting colorless solid (0.29 g, 85%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.40-7.24 (m, 5H), 6.08 (d, *J* = 8.5 Hz,



1H), 5.15 (m, 1H), 3.07 (m, 2H), 1.98 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 169.6, 134.1, 129.6, 129.2, 128.2, 118.3, 41.7, 38.9, 23.0. Spectral data was consistent with literature.<sup>18</sup>

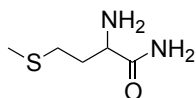


**(L)-3-Phenyl-2-(propylamino)propanenitrile (1w).** Enantiopure  $\alpha$ -aminonitrile starting material was obtained using a modified procedure from Rodriguez.<sup>8</sup> (*L*)-2-amino-3-phenylpropanamide HCl (2.00 g, 10.0 mmol) and Et<sub>3</sub>N (2.92 mL, 21.0 mmol) was dissolved in acetonitrile (10 mL). The mixture was cooled to 0 °C and allyl bromide (0.86 mL, 10.0 mmol) was added dropwise. The solution was warmed to rt and stirred for 14 hours. The mixture was diluted with 1:1 mixture of sodium bicarbonate : brine (20 mL) and extracted with EtOAc (5 x 30 mL). The organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure giving a crude solid. Purification by column chromatography (EtOAc/MeOH, 95:5, TLC R<sub>f</sub> = 0.29) provided (*L*)-2-(allylamino)-3-phenylpropanamide (0.51 g, 25%): <sup>1</sup>H-NMR (400 MHz; CDCl<sub>3</sub>): δ 7.31-7.19 (m, 5H), 7.06 (s, 1H), 6.07 (s, 1H), 5.64 (dddd, *J* = 17.0, 10.5, 6.4, 5.3 Hz, 1H), 5.02-4.97 (m, 2H), 3.33 (dd, *J* = 9.5, 4.3 Hz, 1H), 3.21-3.13 (m, 2H), 3.05-3.00 (m, 1H), 2.73 (dd, *J* = 13.8, 9.5 Hz, 1H), 1.46 (s, 1H); <sup>13</sup>C NMR (101 MHz; CDCl<sub>3</sub>): δ 177.1, 137.4, 135.8, 129.1, 128.8, 127.0, 116.3, 63.1, 50.9, 39.3. [ $\alpha$ ]<sub>D</sub><sup>20</sup> -27° (*c* 0.7, CH<sub>2</sub>Cl<sub>2</sub>). (*L*)-2-amino-3-phenylpropanamide was recovered by flushing the column with EtOAc:MeOH mixture (80:20, TLC R<sub>f</sub> = 0.23). The above procedure was repeated a total of 3 times. (*L*)-2-(Allylamino)-3-phenylpropanamide (1.72 g, 8.4 mmol) and sodium bicarbonate (0.62 g, 10.1 mmol) were dissolved in a 1:1 H<sub>2</sub>O/dioxane mixture (34 mL). The solution was cooled to 0 °C and benzyl chloroformate (1.44 mL, 10.1 mmol) was added dropwise. The solution was warmed to rt and stirred for 14 hours. The mixture was diluted with EtOAc (80 mL) and washed with water (40 mL) and brine (2 x 40 mL). The organic layer was dried with sodium sulfate and concentrated under reduced pressure to give the crude product as a colourless oil. Purification by column chromatography (Et<sub>2</sub>O to Et<sub>2</sub>O/EtOAc, 90:10, TLC R<sub>f</sub> = 0.34) provided (*L*)-benzyl allyl(1-amino-1-oxo-3-phenylpropan-2-yl)carbamate as a white solid (0.85 g, 77%): IR (film): 1683, 1662, 1558, 1265, 732, 698. <sup>1</sup>H-NMR (300

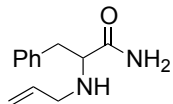
MHz; DMSO- $d_6$ , 80 °C):  $\delta$  7.36-7.17 (m, 10H), 6.96 (s, 2H), 5.72-5.59 (m, 1H), 5.07 (s, 2H), 4.98 (td,  $J = 10.6, 1.4$  Hz, 2H), 4.60 (dd,  $J = 9.0, 6.1$  Hz, 1H), 3.94-3.87 (m, 1H), 3.69 (dd,  $J = 15.9, 6.3$  Hz, 1H), 3.25 (dd,  $J = 14.1, 6.1$  Hz, 1H), 2.98 (dd,  $J = 14.1, 9.2$  Hz, 1H).;  $^{13}\text{C}$ -NMR (76 MHz; DMSO- $d_6$ ):  $\delta$  172.0, 155.9, 138.8, 137.3, 135.5, 129.5, 128.68, 128.5, 128.1, 127.8, 126.6, 116.7, 66.9, 61.3, 48.9, 35.7. HRMS (EI): Exact mass calcd for  $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_3$  [ $\text{M}^+$ ], 338.1630; Found 338.1596 [ $\alpha$ ] $^{20}_{\text{D}}$  -125° ( $c$  1.17,  $\text{CH}_2\text{Cl}_2$ ). (*L*)-Benzyl allyl(1-amino-1-oxo-3-phenylpropan-2-yl)carbamate (1.46 g, 4.3 mmol) was dissolved in DMF (5.0 mL) and cooled to 0 °C for the addition of 2,4,6-trichloro-1,3,5-triazine (0.80 g, 4.3 mmol). The mixture was warmed to rt and stirred for 24 h. The solution was subsequently diluted with EtOAc (40 mL) and washed with a 1:1  $\text{H}_2\text{O}$ /brine mixture (3 x 30 mL). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure to give the crude product as a colourless oil. Purification by column chromatography (Hexane/ $\text{Et}_2\text{O}$ , 75:25, TLC  $R_f = 0.27$ ) provided (*L*)-benzyl allyl(1-cyano-2-phenylethyl)carbamate as a colourless oil (0.99 g, 72%): IR (film): 3064, 2242, 1956, 1701, 1455, 1245, 746.  $^1\text{H}$ -NMR (400 MHz; DMSO- $d_6$ ):  $\delta$  7.35-7.22 (m, 10H), 5.73-5.63 (m, 1H), 5.13 (m, 4H), 5.03 (t,  $J = 8.1$  Hz, 1H), 3.93 (ddt,  $J = 16.4, 5.5, 1.4$  Hz, 1H), 3.70-3.64 (m, 1H), 3.24-3.14 (m, 2H).;  $^{13}\text{C}$  NMR (101 MHz; DMSO- $d_6$ ):  $\delta$  154.9, 136.7, 135.7, 133.7, 129.8, 128.95, 128.89, 128.5, 128.1, 127.7, 118.5, 117.9, 67.6, 50.1, 49.7, 37.0. HRMS (EI): Exact mass calcd for  $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_2$  [ $\text{M}^+$ ], 320.1525; Found 320.1512. [ $\alpha$ ] $^{20}_{\text{D}}$  -53° ( $c$  1.38,  $\text{CH}_2\text{Cl}_2$ ). (*L*)-benzyl allyl(1-cyano-2-phenylethyl)carbamate was dissolved in dioxane (30.0 mL). 10 % Palladium on carbon (0.33 g) was added to the solution. The solution was then purged with hydrogen gas for 5 minutes and stirred under a hydrogen atmosphere for 16 h. The solution was then filtered through celite and washed with EtOAc (100 mL) and subsequently concentrated under reduced pressure providing pure (*L*)-2-amino-3-phenylpropanenitrile as a colourless oil (0.751 g, 99%): IR (film): 3319, 2959, 2236, 1558, 1506, 1263, 732.  $^1\text{H}$ -NMR (400 MHz;  $\text{CDCl}_3$ ):  $\delta$  7.30 (dd,  $J = 15.1, 6.8$  Hz, 5H), 3.74 (t,  $J = 6.5$  Hz, 1H), 3.03 (qd,  $J = 15.7, 6.6$  Hz, 2H), 2.80 (dt,  $J = 10.6, 7.3$  Hz, 1H), 2.60-2.54 (m, 1H), 1.48 (td,  $J = 13.8, 7.0$  Hz, 2H), 1.24 (s, 1H), 0.90 (t,  $J = 7.4$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz;  $\text{CDCl}_3$ ):  $\delta$  135.3, 129.5, 128.8, 127.5, 119.9, 52.0, 49.6, 39.5, 22.9, 11.6. HRMS (ESI): Exact mass calculated for  $\text{C}_{11}\text{H}_{16}\text{N}_2$  [ $\text{M}+\text{H}^+$ ] $^+$ , 189.1386; Found 189.1392. [ $\alpha$ ] $^{20}_{\text{D}}$  -31° ( $c$  0.95,  $\text{CH}_2\text{Cl}_2$ ).

### General procedure for formaldehyde-catalyzed hydrolysis of $\alpha$ -aminonitriles:

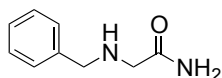
$\alpha$ -Aminonitrile (1.0 mmol) was taken up in H<sub>2</sub>O (1.0 mL). NaOH (5 M, 0.20 mmol, 0.04 mL) was added followed by formalin (0.20 mmol, 14.9  $\mu$ L). The reaction mixture was stirred at rt and monitored by TLC. After completion, the reaction mixture was diluted with H<sub>2</sub>O (2 mL) and EtOAc (10 mL). The aqueous and organic layers were separated, and the aqueous layer was extracted with EtOAc (10 mL x 4). The organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by silica gel chromatography gave the corresponding  $\alpha$ -aminoamide.



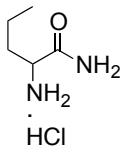
**Methionine amide (3a).** The general procedure was followed with a modified work-up procedure using 2-amino-4-methylthiobutyronitrile (**1a**) (0.13 g, 1.0 mmol). Following reaction completion, the solvent was removed under reduced pressure. The resulting residue was purified by column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/aq NH<sub>4</sub>OH, 89:10:1, TLC  $R_f$  = 0.19) to afford methionine amide (**3a**) as an off-white solid (0.082 g, 56%): mp 49- 50 °C; IR (film): 3325, 3160, 1650, 1438 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O)  $\delta$  3.50 (dd,  $J$ = 7.3, 6.0 Hz, 1 H) 2.56 (t,  $J$  = 7.5 Hz, 2 H) 2.09 (s, 3 H) 1.96-1.88 (m, 1 H) 1.86-1.81 (m, 1 H); <sup>13</sup>C NMR (100 MHz, D<sub>2</sub>O)  $\delta$  180.0, 53.3, 33.4, 29.2, 14.0; HRMS (ESI): Exact mass calcd for C<sub>5</sub>H<sub>12</sub>N<sub>2</sub>OS [M + H]<sup>+</sup>, 149.0749; Found 149.0800. Spectral data was consistent with literature.<sup>19</sup>



***N*-Allylphenylalanine amide (3b).** The general procedure was followed using 2-(*N*-allylamino)-3-phenylpropanenitrile (**1b**) (0.186 g, 1.00 mmol). Purification by silica gel chromatography (EtOAc/MeOH, 95:5, TLC  $R_f$  = 0.25) provided *N*-allylphenylalanine amide (**3b**) as a white solid (0.175 g, 86%): mp 76-78 °C; IR (film) 3319, 3036, 2842, 1640, 962;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.33-7.19 (m, 5H), 7.07 (br s, 1H), 5.91 (br s, 1H), 5.65 (m, 1H), 5.02 (dddd,  $J$  = 7.6, 3.1, 1.5, 1.5 Hz, 1H), 4.98 (m, 1H), 3.34 (dd,  $J$  = 9.5, 4.3 Hz, 1H), 3.22-3.13 (m, 2H), 3.01 (m, 1H), 2.74 (dd,  $J$  = 13.8, 9.5 Hz, 1H), 1.64 (br s, 1H);  $^{13}\text{C}$  NMR (75 Hz,  $\text{CDCl}_3$ )  $\delta$  177.1, 137.5, 135.8, 129.3, 128.9, 127.1, 116.5, 63.2, 51.0, 39.4; HRMS (EI): Exact mass calcd for  $\text{C}_{10}\text{H}_{16}\text{N}_2\text{O}$   $[\text{M}]^+$ , 204.1257; Found 204.1249.

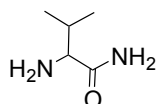


***N*-Benzylglycine amide (3c).** The reaction was carried out following general procedure using commercially available 2-(benzylamino)acetonitrile hydrochloride (0.183 g, 1.00 mmol) and an additional equivalent of NaOH (5 M in  $\text{H}_2\text{O}$ , 1.2 mmol) to neutralize the hydrochloride salt *in situ*. The residue was purified by column chromatography ( $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{aq NH}_4\text{OH}$ , 94:5:1, TLC  $R_f$  = 0.30) and afforded *N*-benzylglycine amide (**3c**) as a white solid (0.164 g, 99%):  $^1\text{H}$  NMR (400 MHz,  $\text{D}_2\text{O}$ , mix of rotamers)  $\delta$  7.38-7.32 (m, 5H) 3.78-3.71 (s, 2H) 3.55 (s, 0.36H), 3.28 (s, 1.64H). Spectral data was consistent with literature.<sup>20</sup>

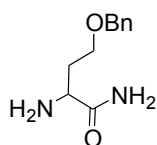


**2-Aminopentanamide hydrochloride salt (3d).** The general procedure was followed using 2-aminopentanenitrile (**1d**) (0.098 g, 1.0 mmol). After completion, the reaction

mixture was acidified with 1N HCl till pH = 1 was achieved. The aqueous layer was then washed with EtOAc (3 x 10 mL). The aqueous layer was then filtered through DOWEX (50X8) and concentrated to give 2-aminopentanamide hydrochloride salt (**3d**) as a pale yellow solid (0.098 g, 64%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 4.02 (t, *J* = 6.4 Hz, 1H), 1.90-1.82 (m, 2H), 1.48-1.35 (m, 2H), 0.95 (t, *J* = 7.2 Hz, 3H). Spectral data was consistent with literature.<sup>21</sup>

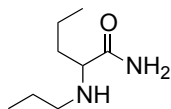


**2-Amino-3-methylbutanamide (3e).** Prepared from 2-amino-3-methylbutyronitrile (**1e**) (0.0980 g, 1.00 mmol) using the general procedure. The crude mixture was purified by flash column chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/aq NH<sub>4</sub>OH, 89:10:1 TLC R<sub>f</sub> = 0.24) to afford 2-amino-3-methylbutanamide (**3e**) as a white solid (0.086 g, 74%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.09 (br s, 1H), 5.85 (br s, 1H), 3.24 (br s, 1H), 2.26 (td, *J* = 3.5, 6.9 Hz, 1H), 1.71 (br. s., 2H), 1.00 (d, *J* = 7.0 Hz, 3H), 0.87 (d, *J* = 6.9 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 177.6, 60.2, 30.8, 19.6, 16.1. Spectral data was consistent with literature.<sup>22</sup>

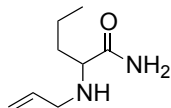


**2-Amino-4-(benzyloxy)butyramide (3f).** Prepared from 2-amino-4-(benzyloxy)butyronitrile (**1f**) (0.285 g, 1.50 mmol) using the general procedure. The crude mixture was purified by flash column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/aq NH<sub>4</sub>OH, 94:5:1, TLC R<sub>f</sub> = 0.25) to provide 2-amino-4-(benzyloxy)butyramide (**3f**) as a yellow oil (0.190 g, 61%): IR (film): 3374, 3199, 3093, 3062, 3032, 2922, 2868, 2796, 1667, 1626, 1496, 1451, 1367 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.28-7.40 (m, 5H) 7.16 (br. s., 1H) 5.49 (br. s., 1H) 4.52 (s, 2H) 3.62-3.74 (m, 2H) 3.55 (dd, *J* = 8.3, 4.2 Hz, 1H) 2.15 (ddt, *J* = 14.6, 7.0, 4.3 Hz, 1H) 1.91-1.71 (m, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 178.4, 138.0, 128.3 (2C), 127.6, 127.5 (2C), 72.9, 68.0, 53.7, 34.5; HRMS (EI): Exact mass calculated for C<sub>10</sub>H<sub>14</sub>NO [M-

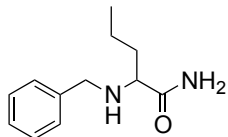
$\text{CH}_2\text{NO}]^+$ , 164.1075; Found 164.1090, exact mass calculated for  $\text{CH}_2\text{NO} [\text{M}-\text{C}_{10}\text{H}_{14}\text{NO}]^+$ , 44.0136; Found : 44.0124.



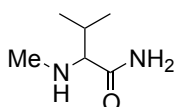
**2-(*N*-Propylamino)pentanamide (3g).** The general procedure was followed using 2-(*N*-propylamino)pentanenitrile (**1g**) (0.50 g, 3.5 mmol). Purification by recrystallization (hexane/EtOAc, 80:20) provided 2-(*N*-propylamino)pentanamide (**3g**) as a white solid (0.351 g, 64%): TLC: EtOAc,  $R_f = 0.25$ ; mp 72-74 °C; IR (film): 3312, 2965, 2872, 1671, 1458, 1136  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.14 (br s, 1H), 5.47 (br s 1H), 3.05 (dd,  $J = 7.7, 5.0$  Hz, 1H), 2.55 (m, 2H), 1.71 (m, 1H), 1.65 (br s, 1H), 1.59-1.34 (m, 5H), 0.94 (t,  $J = 7.3$  Hz, 3H), 0.92 (t,  $J = 7.3$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  178.1, 63.2, 51.1, 36.0, 23.6, 19.5, 14.1, 11.9; HRMS (ESI): Exact mass calcd for  $\text{C}_5\text{H}_{11}\text{N}_2\text{O} [\text{M} - \text{C}_3\text{H}_7]^+$  115.0871; Found 115.0877.



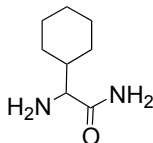
**2-(*N*-Allylamino)pentanamide (3h).** The general procedure was followed using 2-(*N*-allylamino)pentanenitrile (**1h**) (0.500 g, 3.62 mmol). Purification by silica gel chromatography (EtOAc; TLC  $R_f = 0.25$ ) provided 2-(*N*-allylamino)pentanamide (**3h**) as a white solid (0.384 g, 68%): mp 49-50 °C; IR (film): 3080, 2961, 2875, 1663, 1402  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.07 (br s, 1H), 5.85 (dddd,  $J = 17.1, 10.2, 6.4, 5.4$  Hz, 1H), 5.79 (br s, 1H), 5.19 (dddd,  $J = 17.1, 1.6, 1.6, 1.6$  Hz, 1H), 5.11 (dddd,  $J = 10.2, 1.3, 1.3, 1.3$  Hz, 1H), 3.21 (m, 2H), 3.11 (dd,  $J = 7.5, 5.2$  Hz, 1H), 1.97 (br s, 1H), 1.69 (m, 1H), 1.52 (m, 1H), 1.44-1.33 (m, 2H), 0.93 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  177.7, 135.9, 116.7, 62.2, 51.3, 35.8, 19.3, 14.1; HRMS (ESI): Exact mass calcd for  $\text{C}_8\text{H}_{17}\text{N}_2\text{O} [\text{M} + \text{H}^+]$ , 157.1341; Found 157.1313.



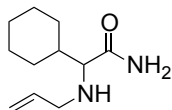
**2-(*N*-Benzylamino)pentanamide (3i):** The general procedure was followed using 2-(*N*-benzylamino)pentanenitrile (**1i**) (0.080 g, 0.43 mmol) in a solvent mixture water/*i*-PrOH (9:1) using 0.35 mmol of formaldehyde (formalin solution, 0.8 equiv.). This reaction was performed twice. Analysis using 1,3,5-trimethoxybenzene as internal standard indicated a 92% NMR yield.<sup>23</sup> Purification of a second reaction by silica gel chromatography provided 2-(*N*-benzylamino)pentanamide (**3i**) as a white solid in quantitative yield: IR (film): 3365, 3210, 2945, 1680, 1458, 1136 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.36-7.25 (m, 5H), 7.18 (br s, 1H), 6.08 (br s, 1H), 3.83 (d, *J* = 13.1 Hz, 1H), 3.7 (d, *J* = 13.1 Hz), 3.44 (br s, 1H), 3.20 (dd, *J* = 7.5, 5.3 Hz, 1H), 1.74 (m, 1H), 1.60 (m, 1H), 1.50–1.38 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H), 0.92 (t, *J* = 7.3 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>/CD<sub>3</sub>OD (9:1) with trimethoxybenzene -TMB) δ 182.2, 165.4 (TMB), 143.4, 132.4, 132.0, 131.2, 96.8 (TMB), 81.3, 65.9, 59.2, 56.5 (TMB), 39.6, 17.7. HRMS (ESI): Exact mass calcd for C<sub>12</sub>H<sub>18</sub>N<sub>2</sub>O [M – Na]<sup>+</sup>, 229.1326; Found 229.1317.



**2-*N*-Methylamino-3-methylbutyramide (3j).** The general procedure was followed using 2-(*N*-methylamino)-3-methylbutyronitrile (**1j**) (0.081 g, 0.071 mmol), using 10 mol% of formaldehyde and maintaining the temperature at 10 °C. Yield was reported using 1,3,5-trimethoxybenzene (TMB) as NMR standard (76%): <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O/DMSO-*d*<sub>6</sub>, 1:1) δ 6.05 (TMB), 3.67 (TMB), 2.53 (d, *J* = 6.5 Hz, 1H), 1.68 (m, 1H), 0.83 (dd, *J* = 6.8, 2.4 Hz, 6H); <sup>13</sup>C NMR (100 MHz, D<sub>2</sub>O/DMSO-*d*<sub>6</sub>, 1:1) δ 177.0, 161.7 (TMB), 93.3 (TMB), 70.1, 55.7 (TMB), 35.1, 31.3, 20.0, 19.3. Spectral data was consistent with literature.<sup>24</sup>



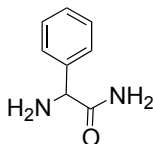
**2-Aminocyclohexylacetamide (3k).** Prepared from 2-amino-2-cyclohexylacetonitrile (**1k**) (0.250 g, 1.81 mmol) using the general procedure (note: stirring the reaction mixture vigorously is important). The crude mixture was purified by flash column chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/aq NH<sub>4</sub>OH, 94:5:1, TLC *R<sub>f</sub>* = 0.23) to afford 2-aminocyclohexylacetamide (**3k**) as a white solid (0.192 g, 68%): mp 144-145 °C; IR (film): 3321, 3156, 2923, 2850, 1699, 1667, 1582 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.05 (br s, 1H), 5.68 (br s, 1H), 3.24 (d, *J* = 4.1 Hz, 1H), 1.94-1.82 (m, 1H), 1.82-1.72 (m, 2H), 1.71-1.57 (m, 3H), 1.53-0.99 (m, 7H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 177.4, 59.7, 40.7, 29.8, 26.4, 26.0, 25.8, 25.7; HRMS (EI): Exact mass calculated for C<sub>7</sub>H<sub>14</sub>N [M-CH<sub>2</sub>NO]<sup>+</sup>, 112.1126; Found 112.1149. Exact mass calculated for CH<sub>2</sub>NO [M-C<sub>7</sub>H<sub>14</sub>N]<sup>+</sup>, 44.0136; Found 44.0132. Spectral data was consistent with literature.<sup>22</sup>



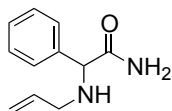
**2-(*N*-Allylamino)-2-cyclohexylacetamide (3l).** 2-(*N*-Allylamino)-2-cyclohexylacetonitrile (**1l**) (1.0 mmol) was taken up in H<sub>2</sub>O (0.5 mL) and CH<sub>3</sub>CN (0.5 mL). NaOH (5 M, 0.20 mmol, 0.040 mL) was added followed by formalin (0.200 mmol, 14.9 μL). The reaction mixture was stirred at rt and monitored by TLC. After completion of the reaction, it was diluted with H<sub>2</sub>O (2 mL) and EtOAc (10 mL). The aqueous and organic layers were separated, and the aqueous layer was extracted with EtOAc (10 mL x 4). The organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by silica gel chromatography (EtOAc to EtOAc/MeOH, 95:5, TLC *R<sub>f</sub>* = 0.25) gave 2-(*N*-allylamino)-2-cyclohexylacetamide (**3l**) as a white solid (80%): mp 81-83 °C; IR (film): 3381, 2925, 2825, 1655, 1406, 1119 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.07 (br s, 1H), 5.85 (dddd, *J* = 17.0, 10.2, 6.6, 5.4 Hz, 1H), 5.62 (br s, 1H), 5.19 (dddd, *J* = 17.1, 1.6, 1.6, 1.6 Hz, 1H), 5.12 (dddd, *J* = 10.2, 1.2, 1.2, 1.2 Hz, 1H), 3.26 (ddt, *J* = 14.3,



5.4, 1.6 Hz, 1H), 3.15 (ddt,  $J = 14.2, 6.6, 1.2$  Hz, 1H), 2.96 (d,  $J = 4.4$  Hz, 1H), 1.88 (br s, 1H), 1.79-1.64 (m, 6H), 1.33-1.03 (m, 5H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  177.0, 136.3, 116.6, 67.7, 52.0, 41.5, 30.4, 28.6, 26.5, 26.5, 26.4; HRMS (ESI): Exact mass calcd for  $\text{C}_{11}\text{H}_{21}\text{N}_2\text{O}$  [ $\text{M}^+ + \text{Na}$ ], 219.1563; Found 219.1529.

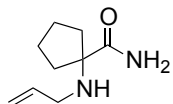


**2-Amino-2-phenylacetamide (3m).** The reaction was carried out following general procedure using commercially available 2-amino-2-phenylacetamide hydrochloride (**1m**). The free base was acquired by dissolving the HCl salt (0.212 g, 1.26 mmol) in a 1:1 mixture of saturated  $\text{NaHCO}_3$  and  $\text{NaCl}$  (5.0 ml) followed by an extraction with EtOAc (3 x 5.0 ml). The organic layers were then combined, dried with sodium sulphate, and concentrated under reduce pressure to provide the desired starting material (0.168 g, 1.20 mmol). The residue of the hydration reaction was purified by column chromatography (EtOAc/MeOH, 80:20, TLC  $R_f = 0.3$ ) to afford 2-amino-2-phenylacetamide (**3m**) as a white solid (0.092 g, 51 %):  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}/\text{CDCl}_3$ )  $\delta$  7.37-7.25 (m, 5H), 4.44 (s, 1H);  $^{13}\text{C}$  NMR (76 MHz; MeOD/ $\text{CDCl}_3$ )  $\delta$  176.3, 140.1, 128.8, 128.1, 126.8, 58.7. Spectral data was consistent with literature.<sup>25</sup>

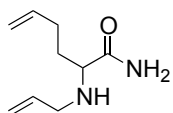


**2-(N-Allylamino)-2-phenylacetamide (3n).** The general procedure was followed using 2-(N-allylamino)-2-phenylacetamide (**1n**) (0.270 g, 1.56 mmol). Purification by silica gel chromatography (EtOAc to EtOAc/MeOH, 95:5, TLC:  $R_f = 0.25$ ) provided 2-(N-allylamino)-2-phenylacetamide (**3n**) as a white solid (0.239 g, 81%): mp 75-76 °C; IR (film): 3322, 3074, 2858, 1651, 1093  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.40-7.27 (m, 5H), 7.00 (br s, 1H), 6.39 (br s, 1H), 5.86 (dddd,  $J = 17.1, 10.2, 6.0, 6.0$  Hz, 1H), 5.18 (dddd,  $J = 17.1, 1.6, 1.6, 1.6$  Hz, 1H), 5.12 (dddd,  $J = 10.2, 1.3, 1.3, 1.3$  Hz, 1H), 4.19 (s,

1H), 3.29-3.20 (m, 2H), 1.98 (br s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 175.5, 139.2, 135.8, 129.0, 128.4, 127.5, 116.9, 66.7, 50.9; HRMS (ESI): Exact mass calcd for C<sub>11</sub>H<sub>15</sub>N<sub>2</sub>O [M + H<sup>+</sup>], 191.1184; Found 191.1217.

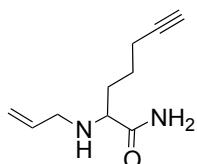


**1-(N-Allylamino)cyclopentanecarboxamide (3o).** The general procedure was followed using 1-(N-allylamino)cyclopentanecarbonitrile (**1o**) (0.150 g, 1.00 mmol) and formalin solution (38 μL, 0.50 mmol). Purification by silica gel chromatography (EtOAc to EtOAc/MeOH, 95:5, TLC R<sub>f</sub> = 0.25) provided 1-(N-allylamino)cyclopentanecarboxamide (**3o**) as a white solid (0.130 g, 77%): mp 53-54 °C; IR (film): 3080, 2871, 1646, 1451, 1090 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.26 (br s, 1H), 5.85 (dddd, J = 17.1, 10.3, 5.6, 5.6 Hz, 1H), 5.48 (br s, 1H), 5.22 (dddd, J = 17.1, 1.7, 1.7, 1.7 Hz, 1H), 5.08 (dddd, J = 10.3, 1.5, 1.5, 1.5 Hz, 1H), 3.11 (m, 1H), 3.09 (m, 1H), 2.17-2.07 (m, 2H), 1.81-1.75 (m, 2H), 1.73-1.63 (m, 4H), 1.49 (br s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 179.7, 136.7, 115.6, 70.1, 47.0, 36.0, 24.5; HRMS (EI): Exact mass calcd for C<sub>6</sub>H<sub>11</sub>NO [M - NCH<sub>2</sub>CHCH<sub>2</sub>]<sup>+</sup>, 113.0841; Found 113.0853.

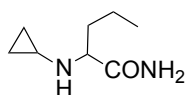


**2-(Allylamino)-5-hexenamide (3p).** Prepared from 2-(N-allylamino)-5-hexenenitrile (**1p**) (0.200 g, 1.33 mmol) using the general procedure. The crude was purified by flash column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/aq NH<sub>4</sub>OH, 96:3:1, TLC R<sub>f</sub> = 0.25) to provide 2-(allylamino)-5-hexenamide (**3p**) as a viscous oil which formed a pale, waxy solid upon refrigeration (0.178 g, 80%): <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.08 (br s, 1H), 5.97-5.75 (m, 2H), 5.60 (br s, 1H), 5.21 (dq, J = 17.2, 1.6 Hz, 1H), 5.14 (dq, J = 10.3, 1.4 Hz, 1H), 5.07 (dq, J = 17.2, 1.6 Hz, 1H), 5.01 (dq, J = 10.2, 1.4 Hz, 1H), 3.33-3.12 (m, 3H), 2.23-2.12 (m, 2H), 2.12-1.93 (m, 1H), 1.88 (dddd, J = 13.9, 8.8, 7.0, 5.3 Hz, 1H), 1.78-1.64 (m, 1

H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  177.0, 137.4, 135.6, 116.8, 115.6, 61.6, 51.0, 32.5, 30.2; IR (neat film, NaCl): 3334, 3328, 3191, 3076, 3003, 2984, 2927, 1841, 1669, 1577, 1455, 1416, 1400, 1333, 1288  $\text{cm}^{-1}$ ; HRMS (EI): Exact mass calculated for  $\text{C}_8\text{H}_{14}\text{N}$   $[\text{M}-\text{CH}_2\text{NO}]^+$ , 124.1126; Found 124.1095; Exact mass calculated for  $\text{CH}_2\text{NO}$   $[\text{M}-\text{C}_8\text{H}_{14}\text{N}]^+$ , 44.0136; Found 44.0094.

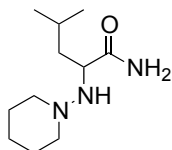


**2-(*N*-Allylamino)hept-6-ynamide (3q).** The general procedure was followed using 2-(*N*-allylamino)hept-6-ynonitrile (**1q**) (0.162 g, 1.00 mmol). Purification by silica gel chromatography (EtOAc, TLC  $R_f$  = 0.25) provided 2-(*N*-allylamino)hept-6-ynamide (**3q**) as a white solid (0.142 g, 79%): mp 88-91 °C; IR (film): 3186, 2954, 2856, 1677, 1458, 1149  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.14 (br s, 1H), 5.96 (br s, 1H), 5.87 (dddd,  $J$  = 16.9, 10.2, 6.4, 5.6 Hz, 1H), 5.22 (dddd,  $J$  = 17.1, 1.5, 1.5, 1.5 Hz, 1H), 5.08 (dddd,  $J$  = 10.2, 1.5, 1.5, 1.5 Hz, 1H), 3.68 (br s, 1H), 3.32-3.18 (m, 3H), 2.23 (m, 2H), 1.96 (t,  $J$  = 2.6 Hz, 1H), 1.81-1.75 (m, 2H), 1.91-1.72 (m, 2H), 1.67-1.60 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  177.2, 135.8, 116.5, 83.8, 69.0, 61.4, 50.8, 32.5, 24.7, 18.2; HRMS (ESI): Exact mass calcd for  $\text{C}_9\text{H}_{14}\text{N}$   $[\text{M} - \text{CONH}_2]^+$ , 136.1126; Found 136.1155.

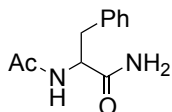


***N*-Cyclopropyl-2-aminopentanamide (3r).** The general procedure was followed using 2-(*N*-cyclopropylamino)pentanenitrile (**1r**) (0.182 g, 1.32 mmol). Purification by silica gel chromatography (EtOAc; TLC  $R_f$  = 0.25) provided *N*-cyclopropyl-2-aminopentanamide (**3r**) as a white solid (0.173 g, 84%): mp 99-100 °C; IR (film): 3092, 3020, 2841, 1680, 1420, 1217;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  6.78 (br s, 1H), 5.59 (br s, 1H), 3.19 (dd,  $J$  = 7.4, 5.2 Hz, 1H), 2.18 (m, 1H), 1.94 (br s, 1H), 1.78-1.67 (m, 1H), 1.60-1.33 (m, 3H), 0.94 (t,  $J$  = 7.2 Hz, 3H), 0.48-0.38 (m, 3H), 0.36-0.30 (m, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$

178.3, 63.2, 35.8, 30.6, 19.3, 14.1, 6.8, 6.4; HRMS (EI): Exact mass calcd for C<sub>8</sub>H<sub>16</sub>N<sub>2</sub>O [M<sup>+</sup>], 156.1263; Found: 156.1269.

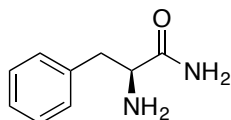


**4-Methyl-2-(piperidin-1-ylamino)pentanamide (3s).** Prepared from 2-amino-4-methylvaleronitrile (**1s**) (0.195 g, 1.00 mmol) using formalin solution (0.50 mmol, 38  $\mu$ L). The crude product was purified by flash column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/aq NH<sub>4</sub>OH, 96:3:1; TLC  $R_f$  = 0.23) to afford 4-methyl-2-(piperidinoamino)valeramide (**3s**) as an amorphous white solid (0.131 g, 61 %); IR (neat film, NaCl): 3346, 3337, 2935, 2860, 2726, 2695, 2671, 1679, 1576, 1525, 1469, 1452, 1367, 1266 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  6.92 (br. s., 1H), 6.25 (br s, 1H), 3.31 (dd,  $J$  = 8.4, 5.5 Hz, 1H), 2.91-2.42 (m, 5H), 1.81-1.69 (m, 1H), 1.61-1.47 (m, 4H), 1.43-1.24 (m, 4H), 0.92 (d,  $J$  = 3.2 Hz, 3H), 0.90 (d,  $J$  = 3.3 Hz, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>)  $\delta$  177.9, 61.1, 58.0, 42.1, 26.9, 25.7, 24.8, 23.6, 22.7; HRMS (ESI): Exact mass calculated for C<sub>11</sub>H<sub>23</sub>N<sub>3</sub>O [M+H]<sup>+</sup>, 214.1919; Found 214.1898.

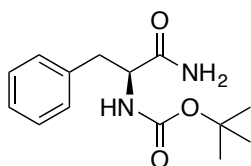


**2-Acetamido-3-phenylpropanamide (3t).** The general procedure was followed using *N*-(1-cyano-2-phenylethyl)acetamide (**1t**) (0.188 g, 1.00 mmol). Purification by silica gel chromatography (EtOAc/MeOH, 80:20; TLC  $R_f$  = 0.53) provided 2-acetamido-3-phenylpropanamide (**3t**) as a white solid (0.146 g, 71%); <sup>1</sup>H-NMR (300 MHz; CD<sub>3</sub>OD/CDCl<sub>3</sub>):  $\delta$  7.22-7.15 (m, 5H), 4.58 (dd,  $J$  = 7.7, 6.5 Hz, 1H), 3.06 (dd,  $J$  = 13.9, 6.3 Hz, 1H), 2.87 (dd,  $J$  = 13.8, 8.0 Hz, 1H), 1.87 (s, 3H). <sup>13</sup>C-NMR (75 MHz; CD<sub>3</sub>OD / CDCl<sub>3</sub>):  $\delta$  174.5, 171.4, 136.6, 129.0, 128.3, 126.7, 54.1, 37.8, 22.1. Spectral data was consistent with literature.<sup>26</sup>

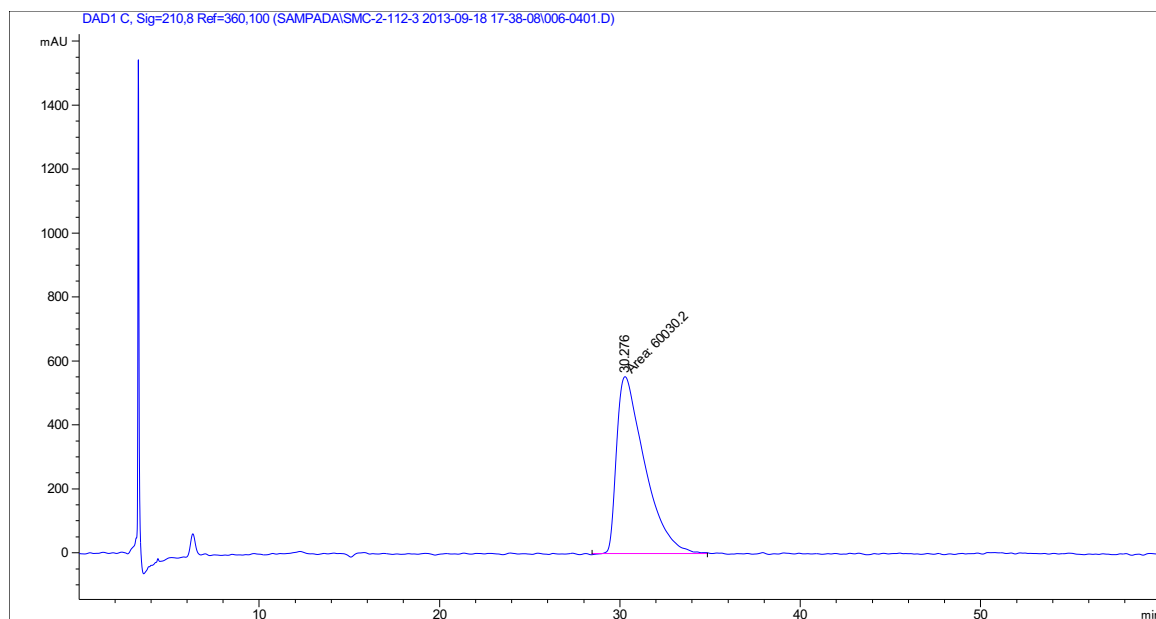




**(L)-Phenylalanine amide (3v).** The reaction was carried out following general procedure using (L)-2-amino-3-phenylpropanitrile (**1v**) (0.146 g, 1.0 mmol).<sup>5</sup> The residue was purified by column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/aq NH<sub>4</sub>OH, 89:10:1, TLC R<sub>f</sub> = 0.25) to afford (L)-phenylalanine amide (**3v**) as a white solid (0.095 g, 65%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>/MeOD-d<sub>4</sub>, 9:1) δ 7.32-7.17 (m, 5H) 3.56-3.52 (m, 1H + 4NH's) 3.13 (dd, *J* = 13.7, 4.7 Hz, 1H) 2.73 (dd, *J* = 13.7, 9.0 Hz, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>/MeOD-d<sub>4</sub>, 9:1) δ 178.0, 137.4, 129.2, 128.7, 126.9, 56.1, 41.0. Spectral data was consistent with literature.<sup>27</sup> (L)-Phenylalanine amide (**3v**) was then derivatized to examine the enantiopurity.

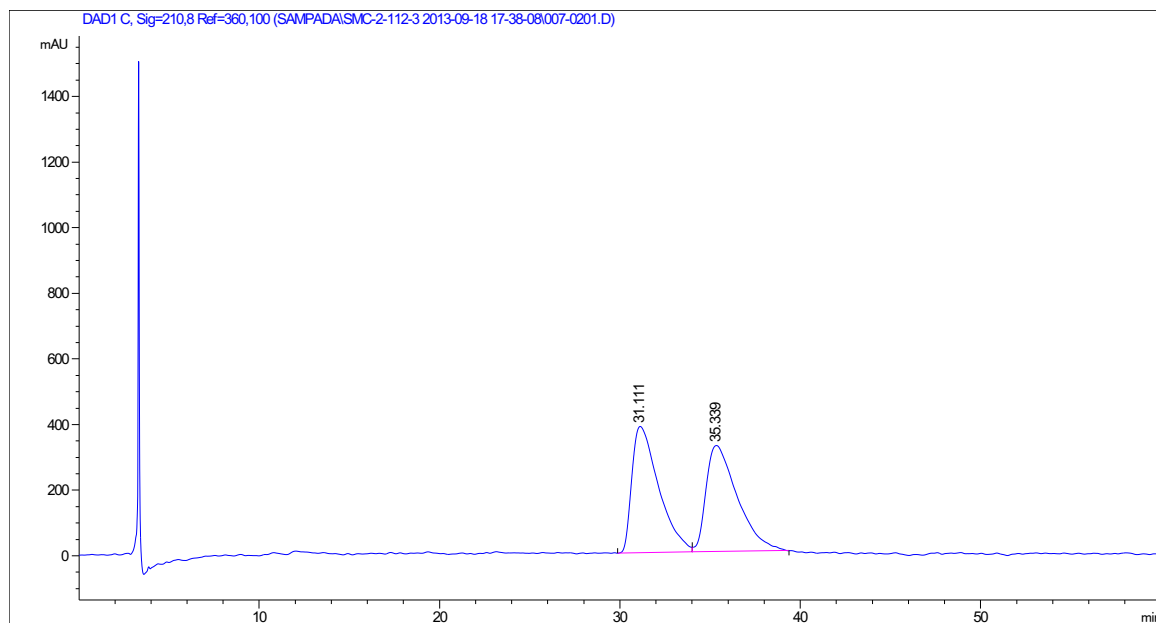


**(L)-N-t-(Butoxycarbonyl)phenylalanine amide (Boc-3v).** (L)- $\alpha$ -Phenylalanine amide (**3v**) (0.090 g, 0.58 mmol) was taken up in *t*-BuOH (1.0 mL). NaOH (0.12 mmol, 0.02 mL) was added followed by di-*t*-butyl dicarbonate (0.253 g, 1.20 mmol). The reaction mixture was stirred at rt overnight. The solvent was then evaporated under reduced pressure. The crude was recrystallized with Hexane/EtOAc (50:50). The white solid was triturated with ice-cold EtOAc to give (L)-*N*-*t*-(butoxycarbonyl)phenylalanine amide (**Boc-3v**) as a white solid (0.128 g, 92%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>/MeOD-d<sub>4</sub>, 9:1) δ 7.31-7.15 (m, 5H) 4.29 (m, 1H), 3.03 (m, 1H) 2.88 (m, 1H), 1.33 (s, 9H); Spectral data was consistent with literature.<sup>28</sup> Chiral HPLC: ChiralPak OD-H, *i*PrOH/hexane = 3:97, 1.0 mL/min, 210 nm, *t* = 30.2 min.



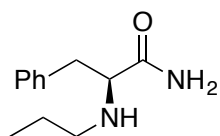
#	Time	Area	Height	Width	Area%	Symmetry
1	30.276	60030.2	554.1	1.8056	100.000	0.415

**Figure S1.** HPLC trace of (L)-*N*-*t*-(butoxycarbonyl)phenylalanine amide shows greater than 99% ee.

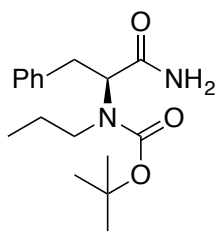


#	Time	Area	Height	Width	Area%	Symmetry
1	31.111	39941.8	385.4	1.523	50.494	0.421
2	35.339	39160.9	323.9	1.6968	49.506	0.47

**Figure S2.** HPLC trace of racemic *N*-*t*-(butoxycarbonyl)phenylalanine amide.



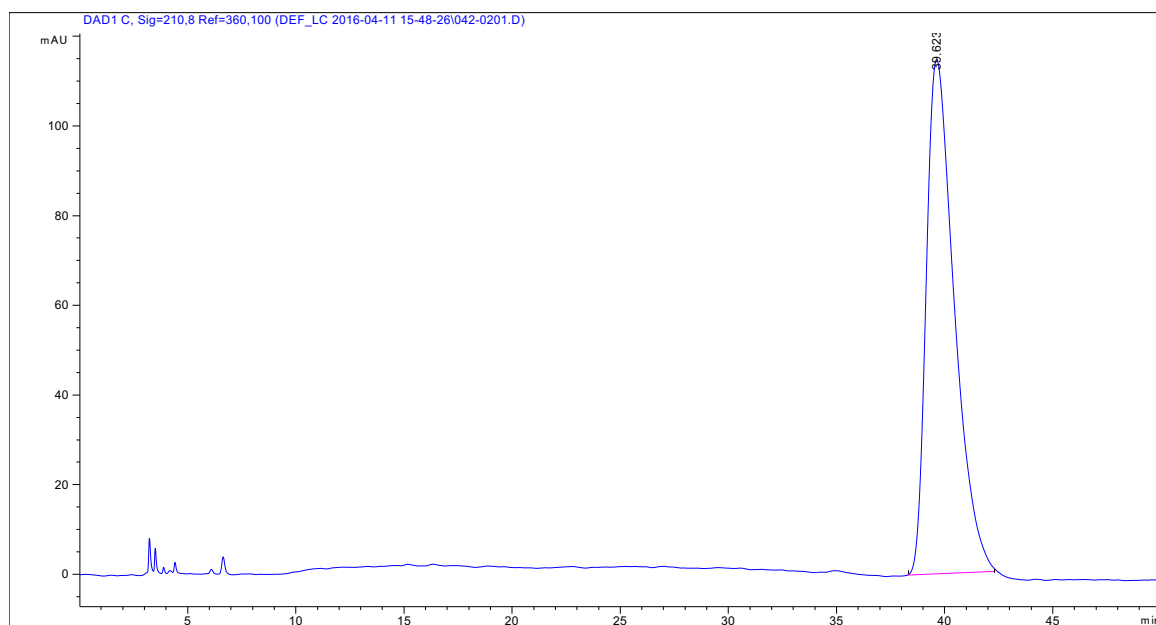
**(L)-3-phenyl-2-(propylamino)propanamide (3w).** The general procedure was followed using (*L*)-3-phenyl-2-(propylamino)propanenitrile (**1w**) (0.122 g, 0.66 mmol) (note: rigorous stirring was necessary for reaction to proceed to completion). Purification by silica gel chromatography (EtOAc/MeOH, 95:5, TLC  $R_f$  = 0.27) provided (*L*)-3-phenyl-2-(propylamino)propanamide (**3w**) as a white solid (0.103 g, 76%): IR (film): 1558, 1265, 736, 727, 700  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.30-7.18 (m, 5H), 7.14 (d,  $J$  = 0.6 Hz, 1H), 6.34 (dd,  $J$  = 0.7, 0.2 Hz, 1H), 3.25 (d,  $J$  = 9.7 Hz, 2H), 2.68 (dd,  $J$  = 13.7, 9.7 Hz, 1H), 2.40 (d,  $J$  = 18.7 Hz, 2H), 1.29 (q,  $J$  = 7.2 Hz, 3H), 0.73 (t,  $J$  = 7.4 Hz, 3H);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  177.6, 137.7, 129.1, 128.8, 126.9, 64.1, 50.6, 39.3, 23.0, 11.5; HRMS (ESI): Exact mass calculated for  $\text{C}_{12}\text{H}_{19}\text{N}_2\text{O}$  [ $\text{M}+\text{H}^+$ ] $^+$ , 207.14912; Found 207.1497.  $[\alpha]_D^{20}$  -30 ( $c$  1.08,  $\text{CH}_2\text{Cl}_2$ ).



**(L)-tert-butyl(1-amino-1-oxo-3-phenylpropan-2-yl)(propyl)carbamate (Boc-3w).** (*L*)-3-phenyl-2-(propylamino)propanamide (0.062 g, 0.30 mmol) was taken up in *t*-BuOH (0.6 mL). NaOH (0.12 mmol, 20 mL) was added followed by di-*t*-butyl dicarbonate (0.131 g, 2.00 mmol). The reaction mixture was stirred at room temperature overnight. The solvent was then evaporated under reduced pressure. The crude was purified by column chromatography ( $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ , 90:10, TLC  $R_f$  = 0.10) provided (*L*)-*tert*-butyl (1-amino-1-oxo-3-phenylpropan-2-yl)(propyl)carbamate (**Boc-3w**) as a colourless oil (0.072 g, 78%): IR (film): 1683, 1652, 1558, 1265, 730, 702  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (300 MHz;  $\text{DMSO-d}_6$ ,

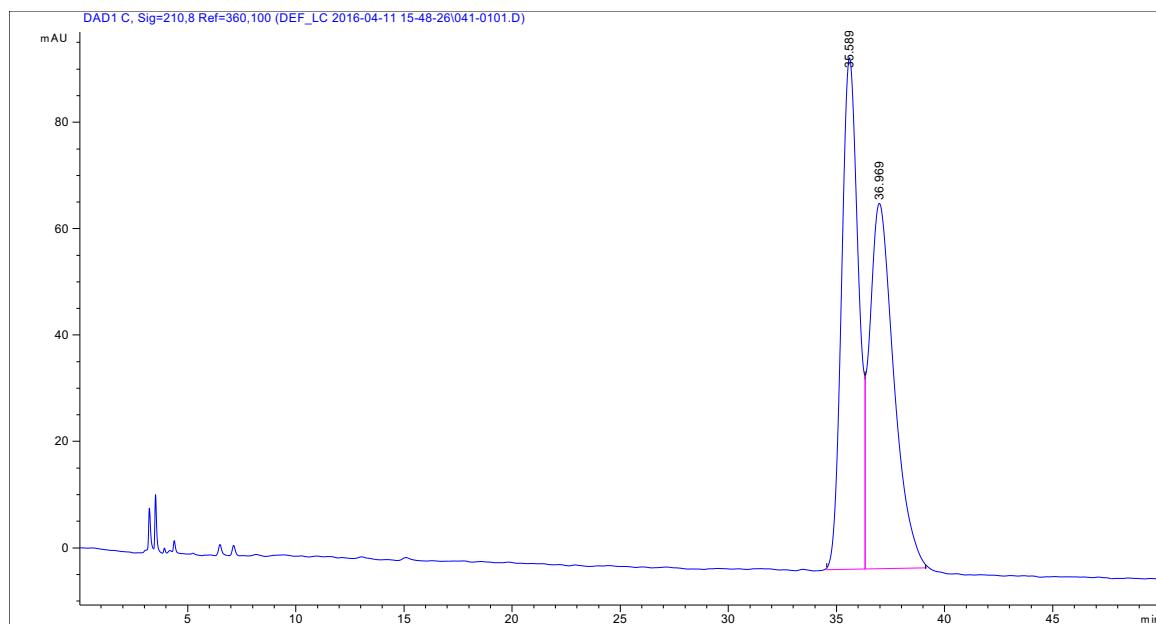


80 °C):  $\delta$  7.28-7.17 (m, 5H), 6.80 (s, 2H), 4.48-4.43 (m, 1H), 3.20 (dd,  $J = 14.0, 6.1$  Hz, 1H), 3.07-2.91 (m, 3H), 1.38 (s, 11H), 0.73 (t,  $J = 7.4$  Hz, 3H);  $^{13}\text{C}$  NMR (76 MHz; DMSO- $d_6$ , 80 °C):  $\delta$  172.6, 155.2, 139.1, 129.5, 128.5, 126.5, 79.4, 61.5, 48.3, 35.8, 28.5 (3C), 22.2, 11.6; HRMS (ESI): Exact mass calcd for  $\text{C}_{17}\text{H}_{26}\text{N}_2\text{O}_3$   $[\text{M} - \text{Na}]^+$ , 329.1836; Found 329.1841.  $[\alpha]_{\text{D}}^{20}$   $-50^\circ$  ( $c$  1.12,  $\text{CH}_2\text{Cl}_2$ ). Chiral HPLC: ChiralPak AD-H,  $i\text{PrOH}/\text{hexane} = 2:98$ , 1.0 mL/min, 210 nm,  $t = 39.6$  min.



#	Time	Area	Height	Width	Area%	Symmetry
1	39.623	10336.1	114.7	1.3091	100.000	0.548

**Figure S3. HPLC trace of (*L*)-*tert*-butyl(1-amino-1-oxo-3-phenylpropan-2-yl)(propyl)carbamate shows greater than 99% ee.**

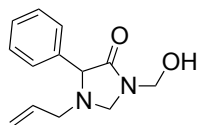


#	Time	Area	Height	Width	Area%	Symmetry
1	35.589	5214.3	96.1	0.8308	49.228	0.853
2	36.969	5377.7	68.7	1.1553	50.772	0.609

**Figure S4.** HPLC trace of racemic *tert*-butyl(1-amino-1-oxo-3-phenylpropan-2-yl)(propyl)carbamate.

### Imidazolidinone **4o**

The presence of imidazolidinone **4o** was confirmed by independent synthesis and characterizing using following method:

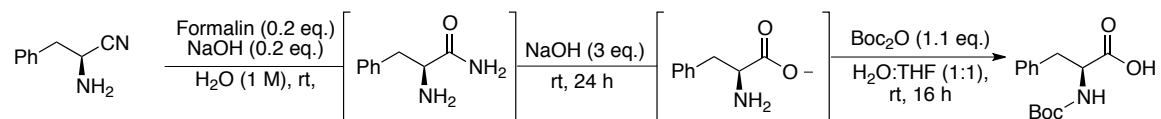


**1-Allyl-3-hydroxymethyl-5-phenylimidazolin-4-one (4n).** (*N*-Allyl)phenylglycinamide (**3n**) (0.10 g, 0.52 mmol) was taken up in H<sub>2</sub>O (0.5 mL). NaOH (0.05 mmol, 10 mL) was then added followed by formalin (0.5 mmol, 0.05 mL). The reaction mixture was stirred at rt for 10 to 12 h. A small amount of starting material was still present. The reaction mixture was then diluted with EtOAc (5 mL) and H<sub>2</sub>O (5 mL). The aqueous and organic layers were

separated, and the aqueous layer was extracted with EtOAc (3 x 5 mL). The organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give the crude product as a colourless oil. Purification by silica gel chromatography (petroleum ether/EtOAc, 50:50, TLC R<sub>f</sub> = 0.25) provided 1-allyl-3-hydroxymethyl-5-phenylimidazol-4-one (**4n**) as a colorless oil (0.031 g, 52% based on formalin): IR (film): 3376 (br), 3067, 2925, 2812, 1708, 1445, 1039 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.45-7.29 (m, 5H), 5.82 (dddd, *J* = 17.2, 10.1, 7.8, 5.0 Hz, 1H), 5.25 (m, 1H), 5.16 (m, 1H), 4.93 (d, *J* = 11.0 Hz, 1H), 4.73 (d, *J* = 11.0 Hz, 1H), 4.59 (dd, *J* = 4.9, 1.2 Hz, 1H), 4.12 (dd, *J* = 4.9, 2.2 Hz, 1H), 4.07 (m, 1H), 3.42 (ddt, *J* = 13.5, 5.0, 1.6 Hz, 1H), 3.04 (dd, *J* = 13.5, 7.8 Hz, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 172.3, 136.7, 133.9, 128.8, 128.4, 128.4, 118.7, 69.5, 66.9, 65.9, 55.7; HRMS (EI): Exact mass calcd for C<sub>13</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub> [M<sup>+</sup>], 232.1212; Found 232.1222.

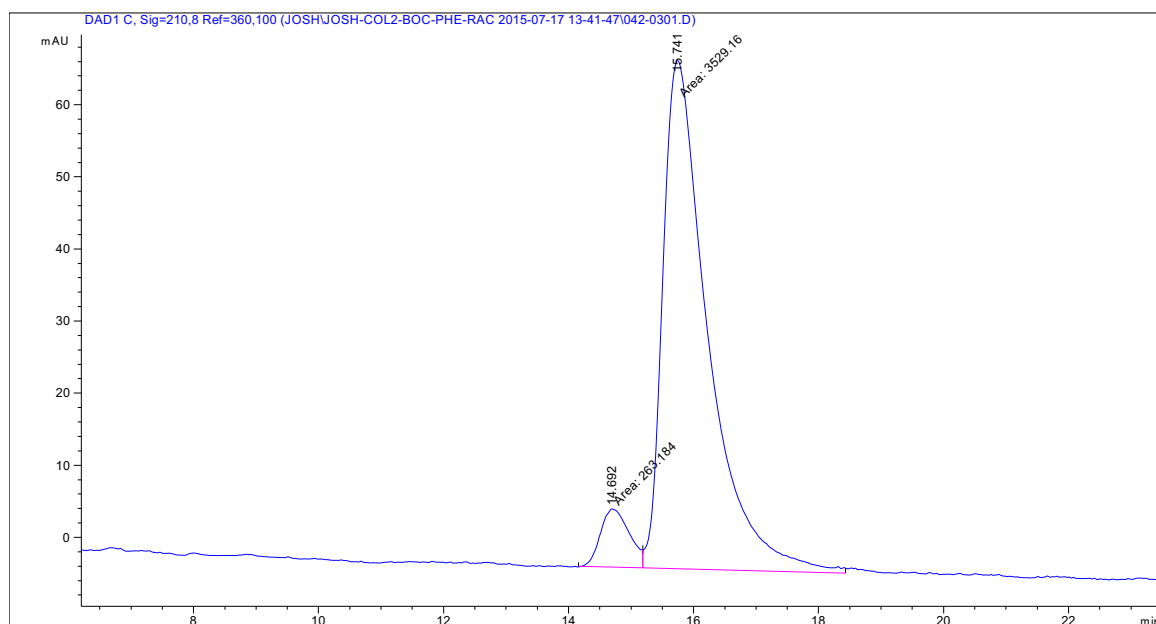
### Procedure for one-pot access to α-amino acids

As indicated in reference 13 of the communication preliminary studies suggest that using excess base with either HCHO or acetone leads to ee erosion. However, hydrolysis of the primary amide can be achieved without ee erosion, in a subsequent step under standard alkaline conditions.



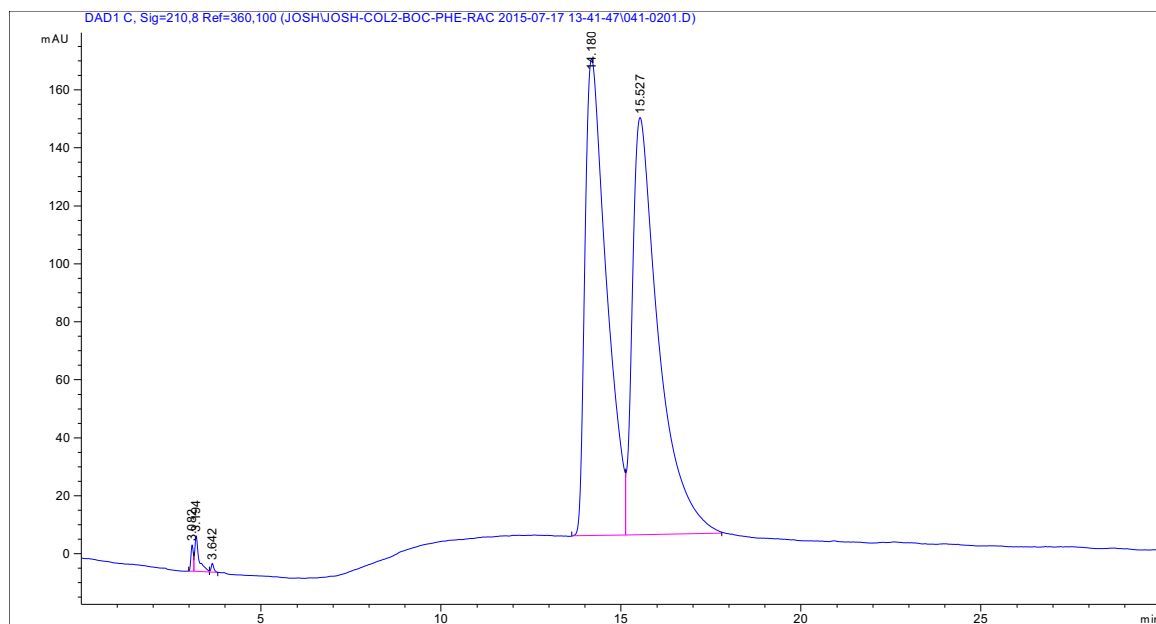
**(L)-2-((tert-Butoxycarbonyl)amino)-3-phenylpropanoic acid (S5a).** (L)-2-Amino-3-phenylpropanenitrile (0.09g, 0.60 mmol) was taken up in H<sub>2</sub>O (0.6 mmol). NaOH (0.12 mmol, 24 mL) was added followed by formalin (0.20 mmol, 8.9 mL). The reaction was stirred at rt and monitored by TLC. After completion of the hydration to amide, H<sub>2</sub>O (0.24 mL) was added to the reaction followed by NaOH (1.8 mmol, 0.36 mL) and stirred for 24 hours. The solution was then diluted with tetrahydrofuran (1.2 mL) followed by the

addition of di-*t*-butyl dicarbonate (0.16 g, 0.72 mmol). The reaction was stirred for 16 hours at which point concentrated HCl was added dropwise until a pH<4 was reached. The solution was diluted with H<sub>2</sub>O (10 mL) and extracted with EtOAc (3 x 10 mL). The organic layers were combined, dried, and concentrated under reduced pressure to provide the product as a crude oil. Purification by silica gel chromatography (CH<sub>2</sub>Cl<sub>2</sub>/Et<sub>2</sub>O, 95:5 to Et<sub>2</sub>O, TLC R<sub>f</sub> = 0.33) provided (*L*)-2-((*tert*-butoxycarbonyl)amino)-3-phenylpropanoic acid (**S5a**) as a colourless oil (0.094 g, 59%): <sup>1</sup>H-NMR (400 MHz; CDCl<sub>3</sub>, rotamers present): δ 9.93 (s, 1H), 7.30-7.16 (m, 5H), 6.43-6.42 (m, 0.3H), 5.05 (d, *J* = 7.9 Hz, 0.6H), 4.60 (d, *J* = 6.8 Hz, 0.6H), 4.38 (s, 0.3H), 3.18 (dd, *J* = 13.6, 5.5 Hz, 1H), 3.05 (dt, *J* = 10.3, 5.0 Hz, 1H), 2.91-2.86 (m, 0.3), 1.40 (s, 6H), 1.29 (s, 3H). Spectral data was consistent with the literature.<sup>29</sup> Chiral HPLC: ChiralPak AD-H, *i*PrOH/hexane = 5:95, 1.0 mL/min, 210 nm, *t* = 15.7 min.



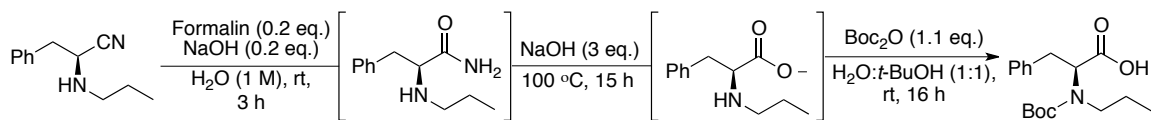
#	Time	Area	Height	Width	Area%	Symmetry
1	14.692	263.2	8.1	0.5406	6.940	0.658
2	15.741	3529.2	70.5	0.8341	93.060	0.467

**Figure S5. HPLC trace of this (*L*)-2-((*tert*-butoxycarbonyl)amino)-3-phenylpropanoic acid shows 86% ee**



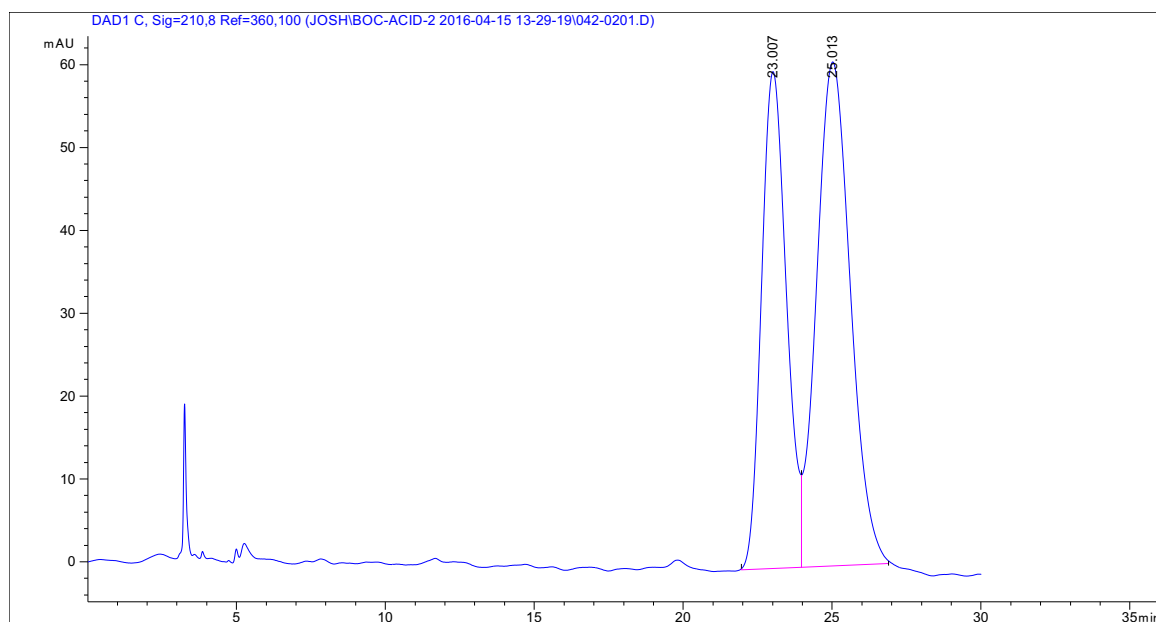
#	Time	Area	Height	Width	Area%	Symmetry
1	14.18	6814.3	164.6	0.6091	48.261	0.412
2	15.527	7305.3	143.9	0.7302	51.739	0.375

**Figure S6. HPLC trace of racemic 2-((*tert*-butoxycarbonyl)amino)-3-phenylpropanoic acid.**



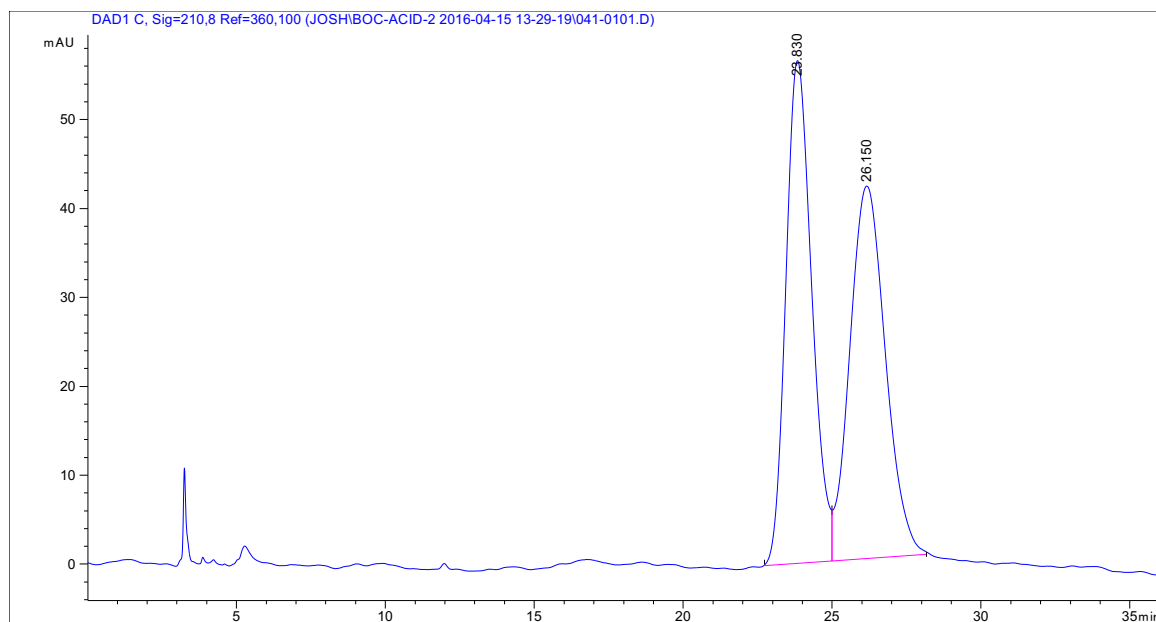
**(*L*)-2-((*tert*-Butoxycarbonyl)(propyl)amino)-3-phenylpropanoic acid (S5b).** (*L*)-3-Phenyl-2-(propylamino)propanenitrile (0.13g, 0.7 mmol) was taken up in H<sub>2</sub>O (0.7 mL). NaOH (0.14 mmol, 28 mL) was added followed by formalin (0.14 mmol, 12.0 μL). The reaction was stirred at rt and monitored by TLC (note: vigorous stirring necessary for reaction to reach completion). After completion of the hydration to amide, H<sub>2</sub>O (0.28 mL) was added to the reaction followed by NaOH (1.8 mmol, 0.43 mL) and refluxed for 15 hours. The solution was then diluted with *t*-BuOH (1.41 mL) followed by the addition of di-*t*-butyl dicarbonate (0.30 g, 1.4 mmol). The reaction was stirred for 16 hours at which point concentrated HCl was added dropwise until a pH<4 was reached. The solution was diluted with H<sub>2</sub>O (15 mL) and extracted with EtOAc (3 x 15 mL). The organic layers were

combined, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure to provide the product as a crude oil. Purification by silica gel chromatography (hexane/ $\text{Et}_2\text{O}$ , 60:40, TLC  $R_f = 0.24$ ) provided (*L*)-2-((*tert*-butoxycarbonyl)(propyl)amino)-3-phenylpropanoic acid (**S5b**) as a colourless oil (0.059 g, 27%):  $^1\text{H-NMR}$  (300 MHz;  $\text{DMSO-d}_6$ , 80 °C):  $\delta$  7.30-7.19 (m, 5H), 4.27-4.22 (m, 1H), 3.23 (dd,  $J = 14.0, 5.3$  Hz, 1H), 3.10 (t,  $J = 7.0$  Hz, 1H), 3.00 (dt,  $J = 14.4, 7.2$  Hz, 1H), 2.69 (dt,  $J = 14.2, 7.2$  Hz, 1H), 1.39 (s, 9H), 1.28 (tq,  $J = 7.4$  Hz, 3H), 0.69 (t,  $J = 7.4$  Hz, 3H);  $^{13}\text{C NMR}$  (76 MHz;  $\text{DMSO-d}_6$ , 80 °C):  $\delta$  172.6, 155.0, 139.2, 129.6, 128.5, 126.5, 79.4, 62.1, 50.3, 36.0, 28.5 (3C), 21.1, 11.5. HRMS (EI): Exact mass calcd for  $\text{C}_{17}\text{H}_{25}\text{N}_2\text{O}_4$  [ $\text{M}^+$ ], 307.1784; Found 307.1812. Chiral HPLC: ChiralPak AD-H, *i*PrOH/hexane = 1:99, 1.0 mL/min, 210 nm,  $t = 23.8$  and 26.2 min.



#	Time	Area	Height	Width	Area%	Symmetry
1	23.007	3489.2	60	0.9088	42.041	0.813
2	25.013	4810.4	60.8	1.2043	57.959	0.864

**Figure S7. HPLC trace of (*L*)-2-((*tert*-butoxycarbonyl)(propyl)amino)-3-phenylpropanoic acid shows 16% ee.**

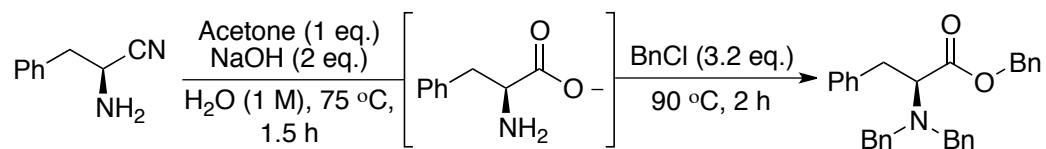


#	Time	Area	Height	Width	Area%	Symmetry
1	23.83	3423	56.6	0.922	49.486	0.78
2	26.15	3494	41.9	1.2365	50.514	0.857

**Figure S8. HPLC trace of racemic 2-((*tert*-butoxycarbonyl)(propyl)amino)-3-phenylpropanoic acid**

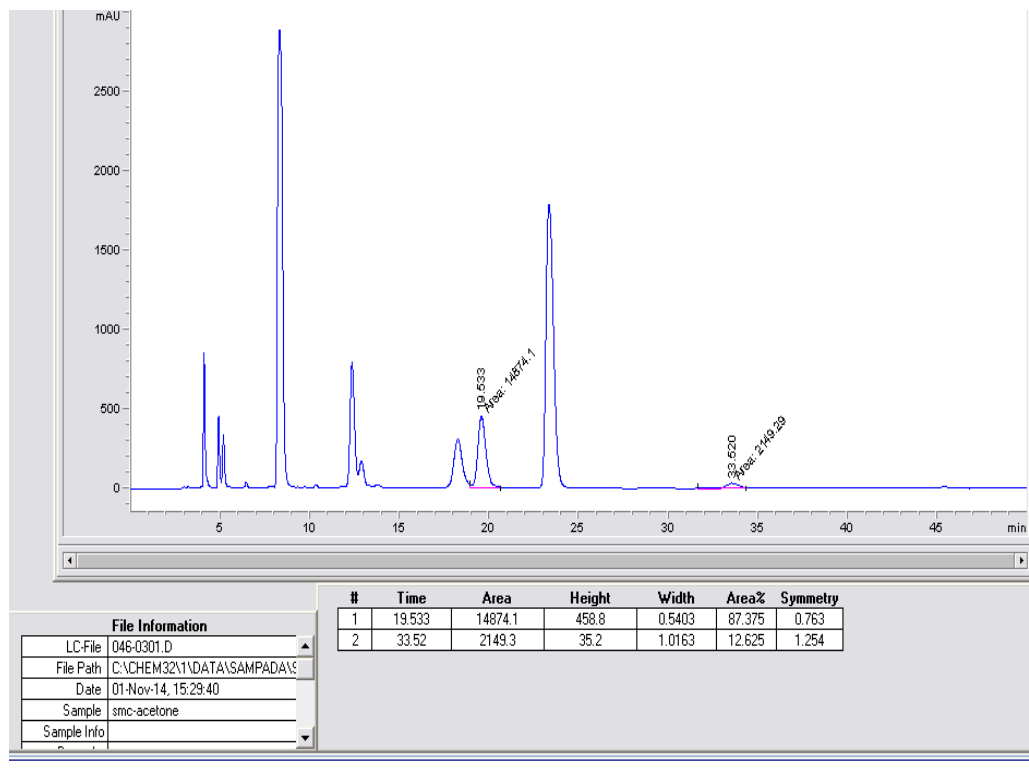
### Comparison with Commeyras' conditions

As indicated in reference 13 of the communication preliminary studies suggest that using excess base with either HCHO or acetone leads to ee erosion. This required a reinvestigation of the conditions of Commeyras' et al. to assess ee erosion under several reaction conditions detailed below.



**(*L*)-Benzyl-2-(dibenzylamino)-3-phenylpropanoate** (*L*)-2-Amino-3-phenylpropano-nitrile was taken up in H<sub>2</sub>O (0.41 mL) followed by the addition of NaOH (0.92 mmol, 0.18

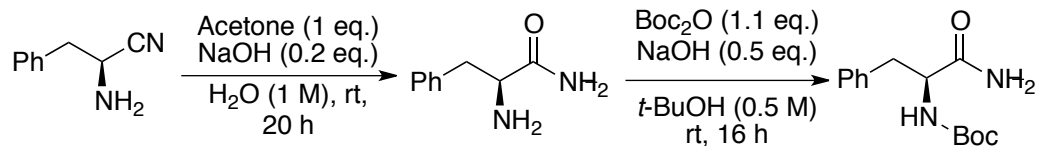
mL) and acetone (0.46 mmol, 0.03 mL). The reaction was subsequently heated to 75 °C for 1.5 h.<sup>30</sup> The reaction was cooled to rt for the addition of benzyl chloride (1.48 mmol, 0.17 mL) and subsequently heated to 90 °C for 2 h. Spectral data was consistent with the literature.<sup>31</sup> Chiral HPLC: ChiralPak AD-H, *i*PrOH/hexane = 2:98, 1.0 mL/min, 210 nm, *t* = 19.5 min.



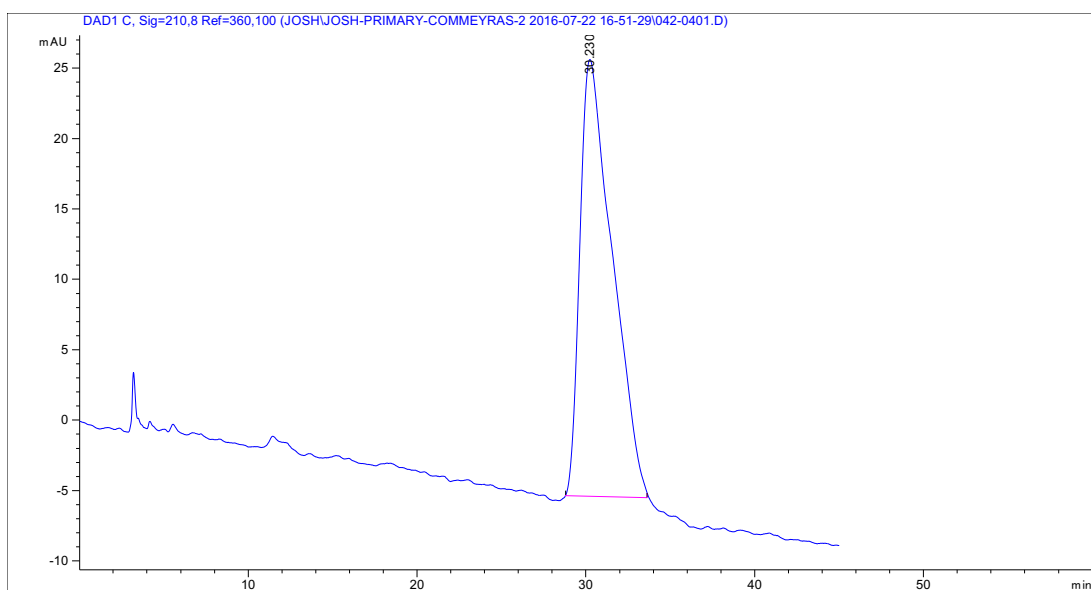
**Figure S9.** Crude HPLC trace of (*L*)-benzyl-2-(dibenzylamino)-3-phenylpropanoate shows 75% ee.





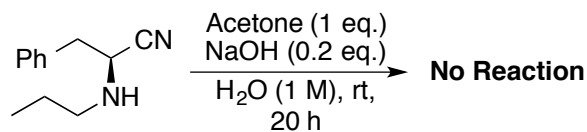


**(L)-*N*-*t*-(Butoxycarbonyl)phenylalanine amide (Boc-6b).** (L)-2-Amino-3-phenylpropionitrile (0.093 g, 0.64 mmol) was taken up in H<sub>2</sub>O (0.64 ml) followed by the addition of NaOH (0.026 mL, 0.28 mmol) and acetone (0.047 mL, 0.64 mmol). The reaction was stirred at room temperature for 2 h.<sup>30</sup> The reaction was subsequently diluted with a saturated sodium bicarbonate solution (2 ml) and extracted with EtOAc (4 x 6 mL). The organic layers were combined and dried down to yield (L)- $\alpha$ -phenylalanine amide (**6b**) as a crude white solid. The crude was then re-suspended in *t*-BuOH (1.3 mL). NaOH (0.13 mmol, 0.026 mL) was added followed by di-*t*-butyl dicarbonate (0.15 ml, 0.70 mmol). Reaction mixture was stirred at rt overnight. Solvent was then evaporated under reduced pressure. The crude was recrystallized with Hexane/EtOAc (50:50). The white solid was triturated with ice-cold EtOAc to give (L)-*N*-*t*-(butoxycarbonyl)phenylalanine amide (**Boc-6b**). Spectral data was consistent with the literature.<sup>28</sup> Chiral HPLC: ChiralPak OD-H, *i*PrOH/hexane = 3:97, 1.0 mL/min, 210 nm, *t* = 30.2 min.



#	Time	Area	Height	Width	Area%	Symmetry
1	30.23	4133.9	31	1.741	100.000	0.415

**Figure S11. HPLC trace of (L)-*N*-*t*-(butoxycarbonyl)phenylalanine amide shows greater than 99% ee.**

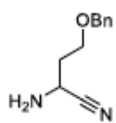


**(L)-tert-Butyl(1-amino-1-oxo-3-phenylpropan-2-yl)(propyl)carbamate.** (L)-3-Phenyl-2-(propylamino)propanenitrile (0.057 g, 0.30 mmol) was taken up in H<sub>2</sub>O (0.3 M) followed by the addition of NaOH (5 M, 0.012 mL, 0.060 mmol) and acetone (0.022 mL, 0.30 mmol). The reaction was vigorously stirred at room temperature.<sup>30</sup> The starting material was present both visually (large oil droplets) and by TLC after 1 h. The reaction was stirred for an additional 18 h with no change. The reaction was subsequently diluted with a saturated sodium bicarbonate solution (1 mL) and extracted with EtOAc (4 x 3 mL). The organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure for NMR analysis which showed pure starting material.

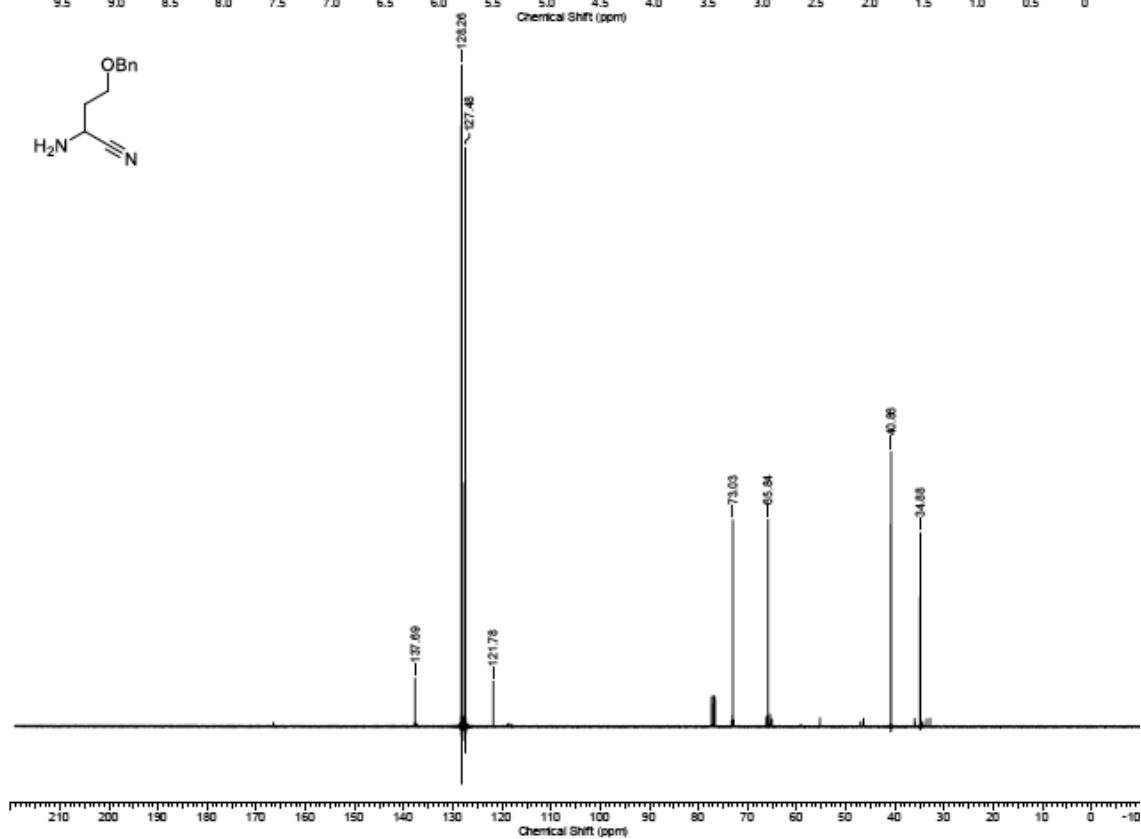
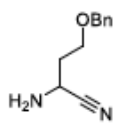
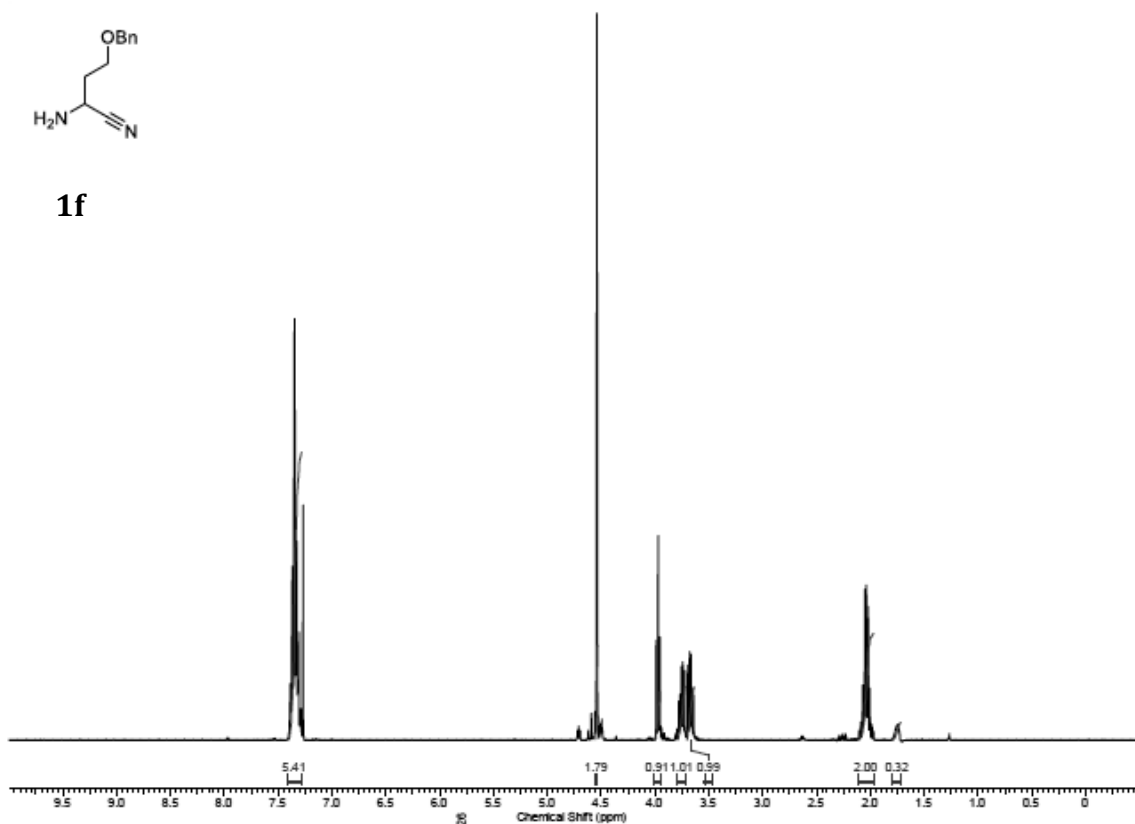
## Reference

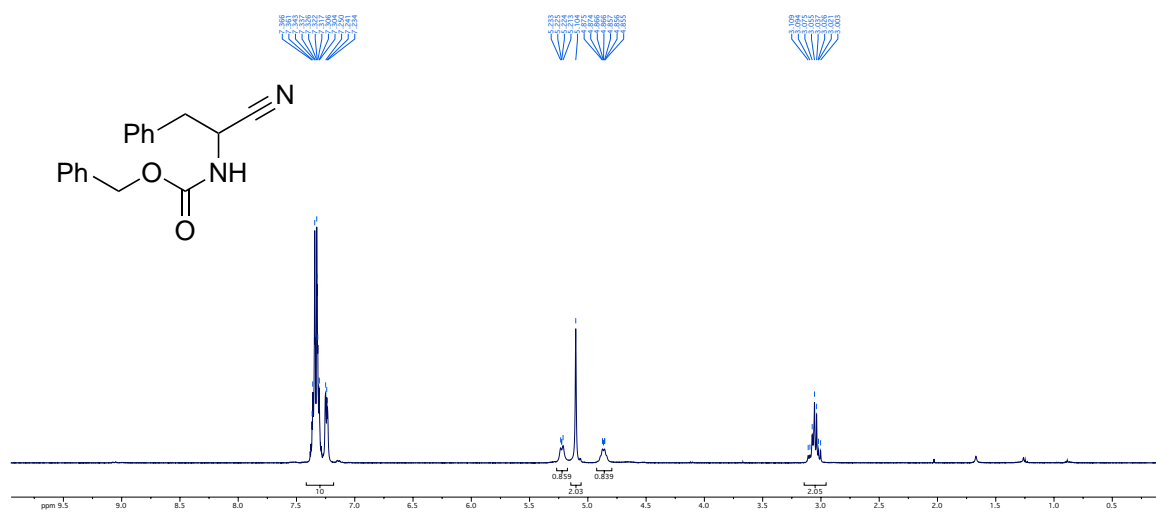
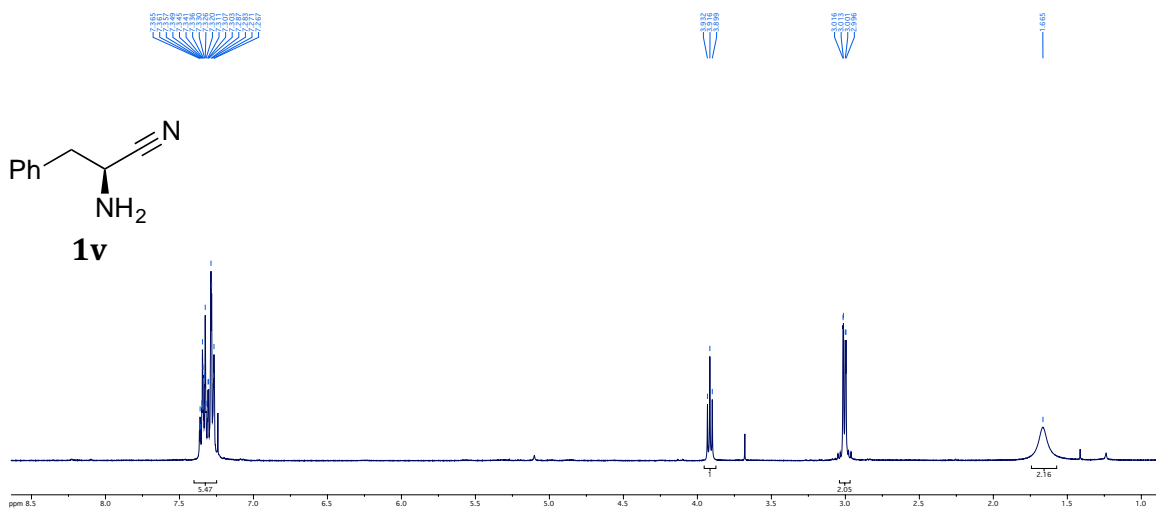
- Over the course of this project, some variability was observed with aged bottles of formalin. For example bottles with a white precipitate (paraformaldehyde) led to variability in reaction results.
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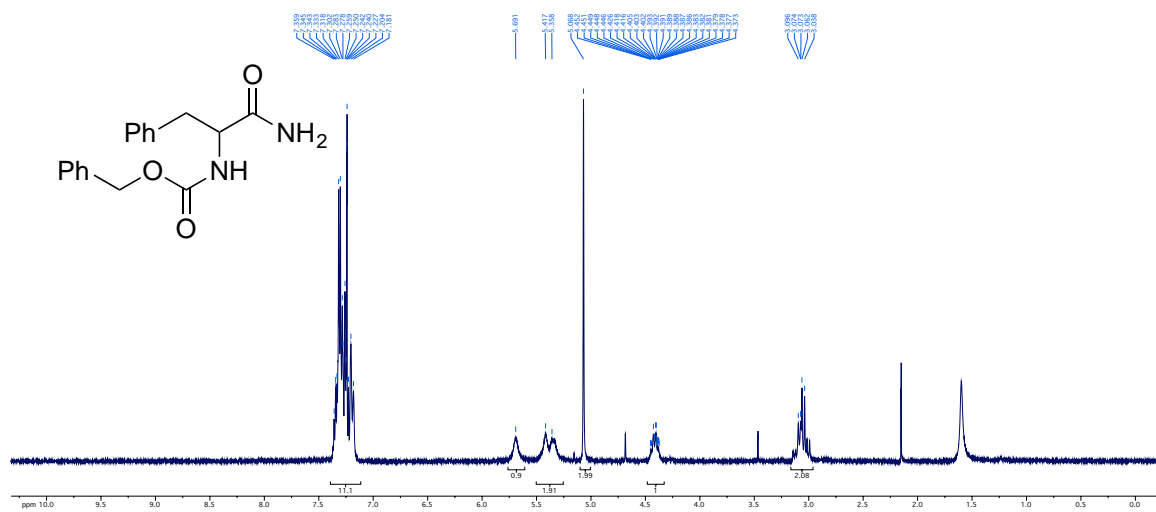
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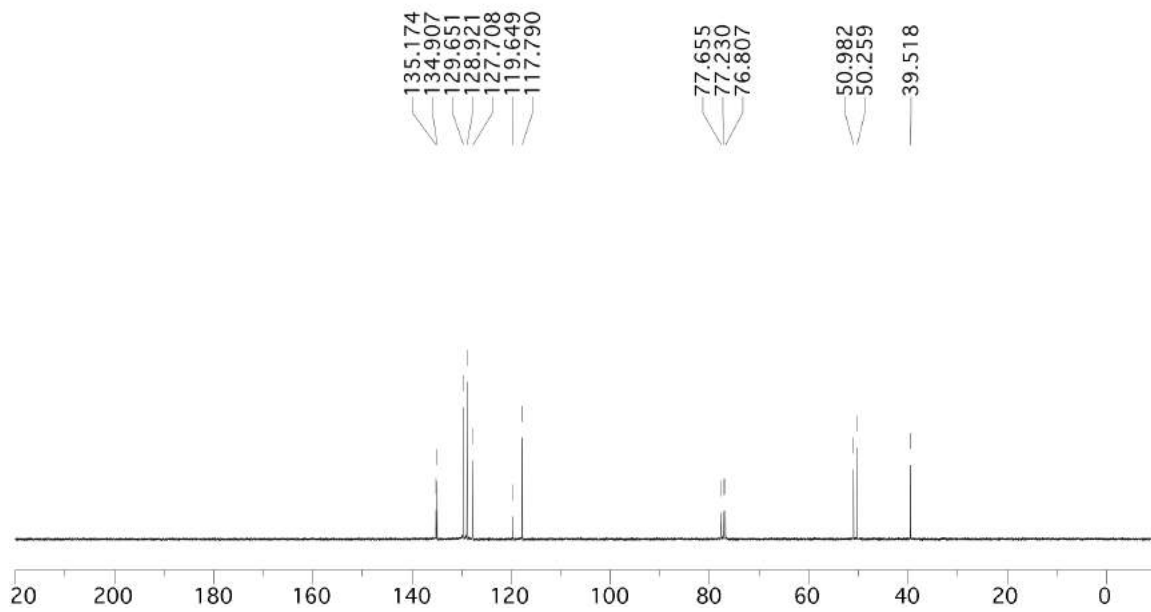
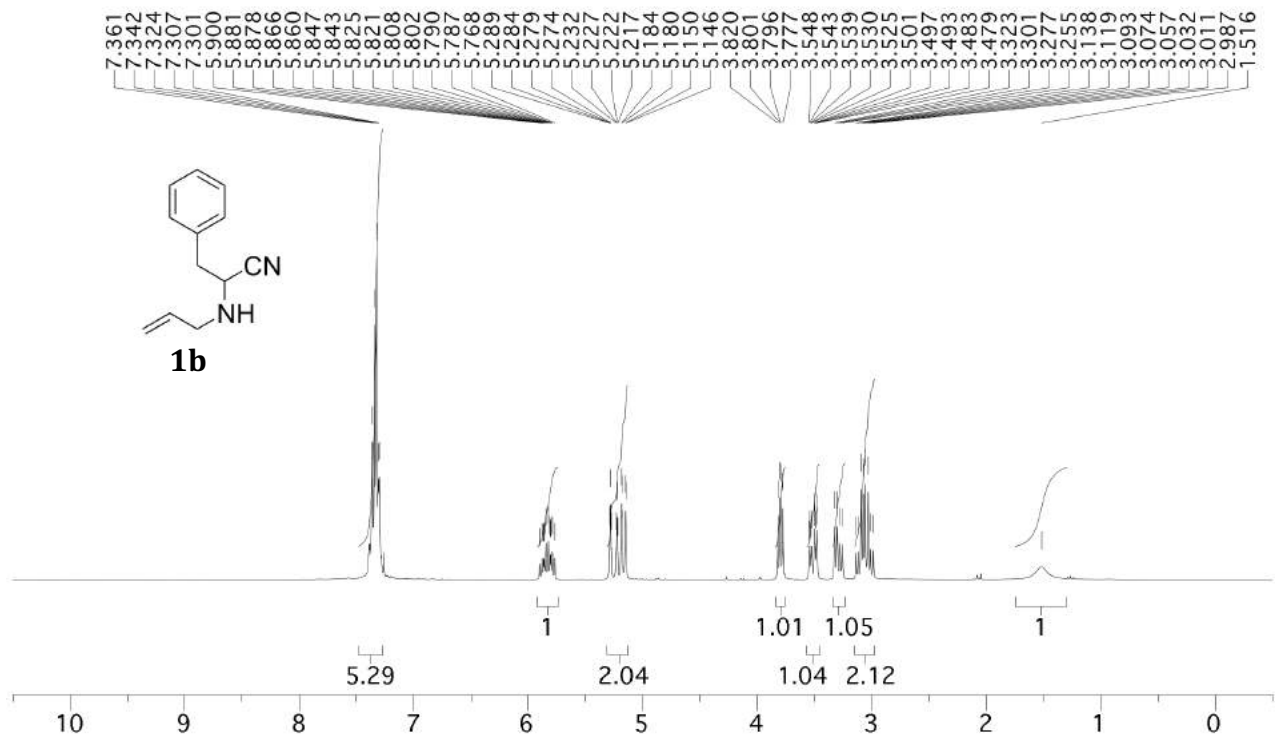


**1f**

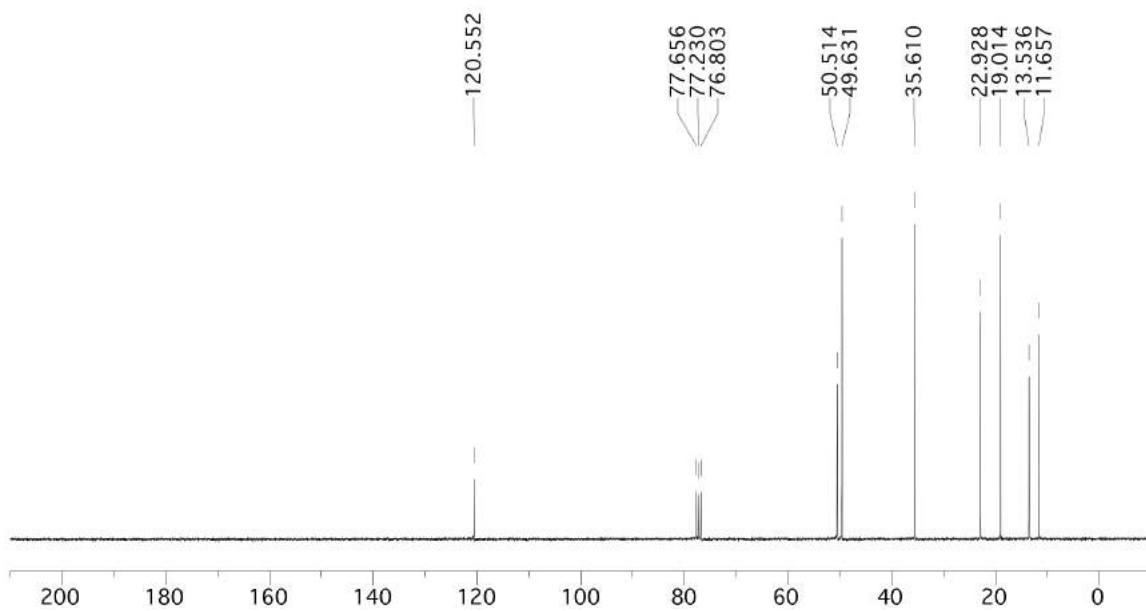
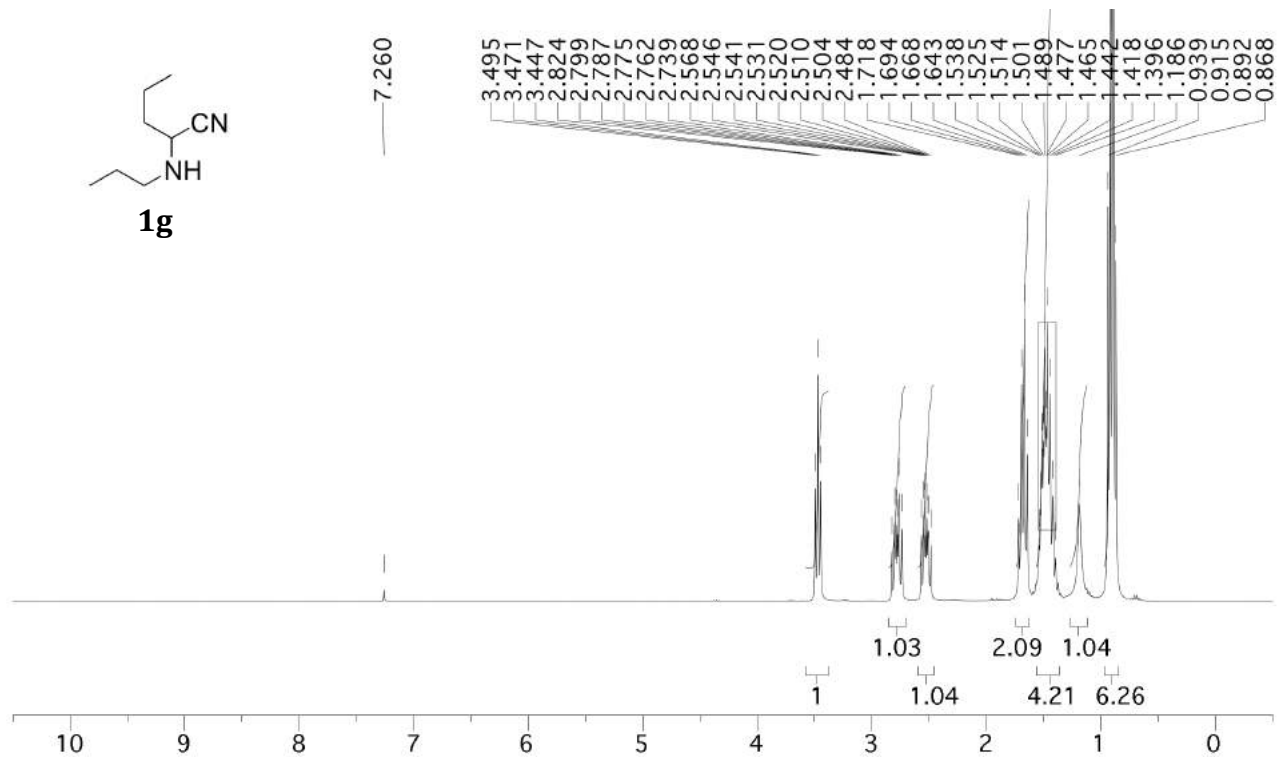
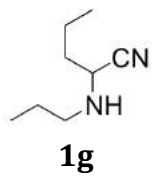


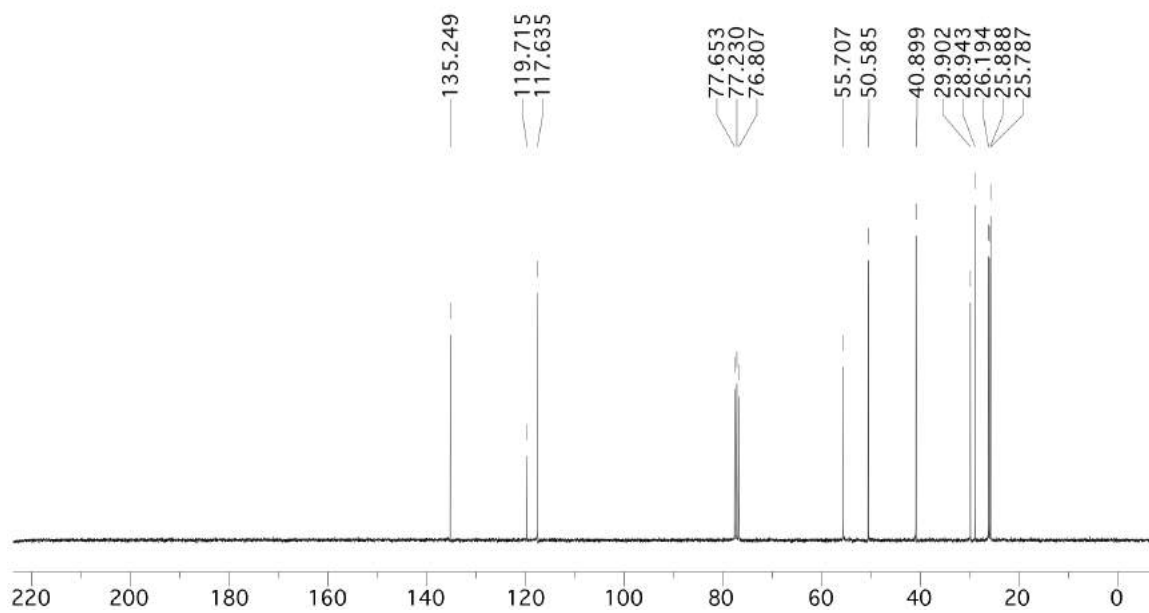
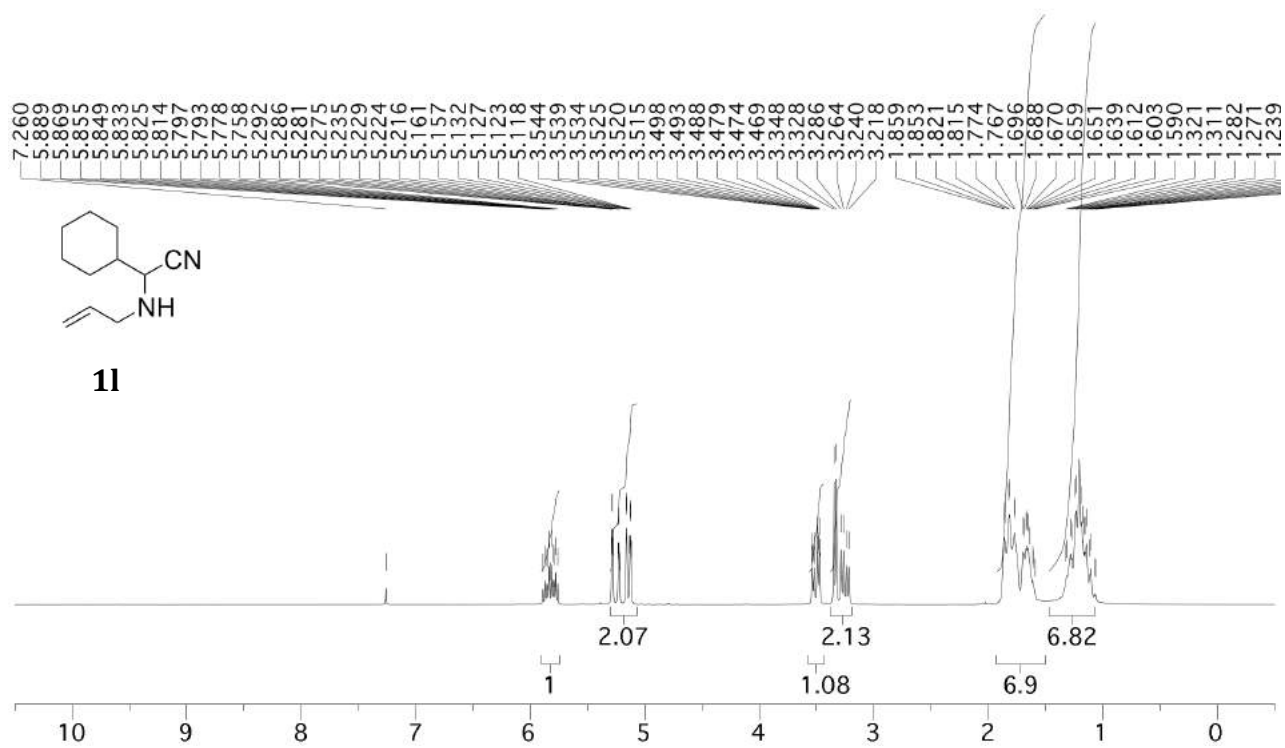


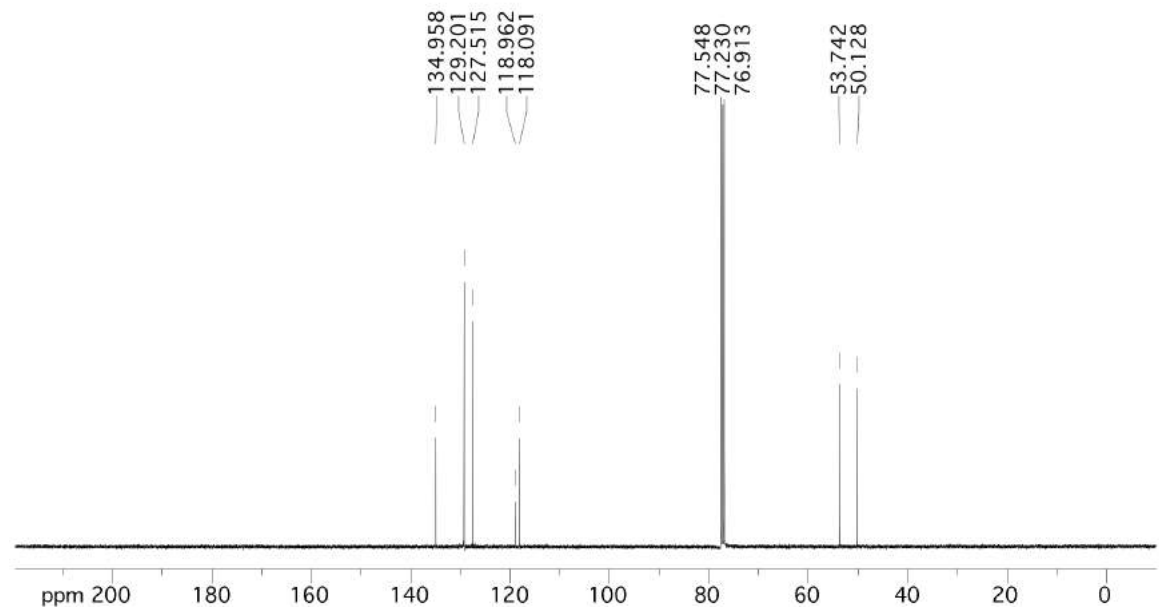
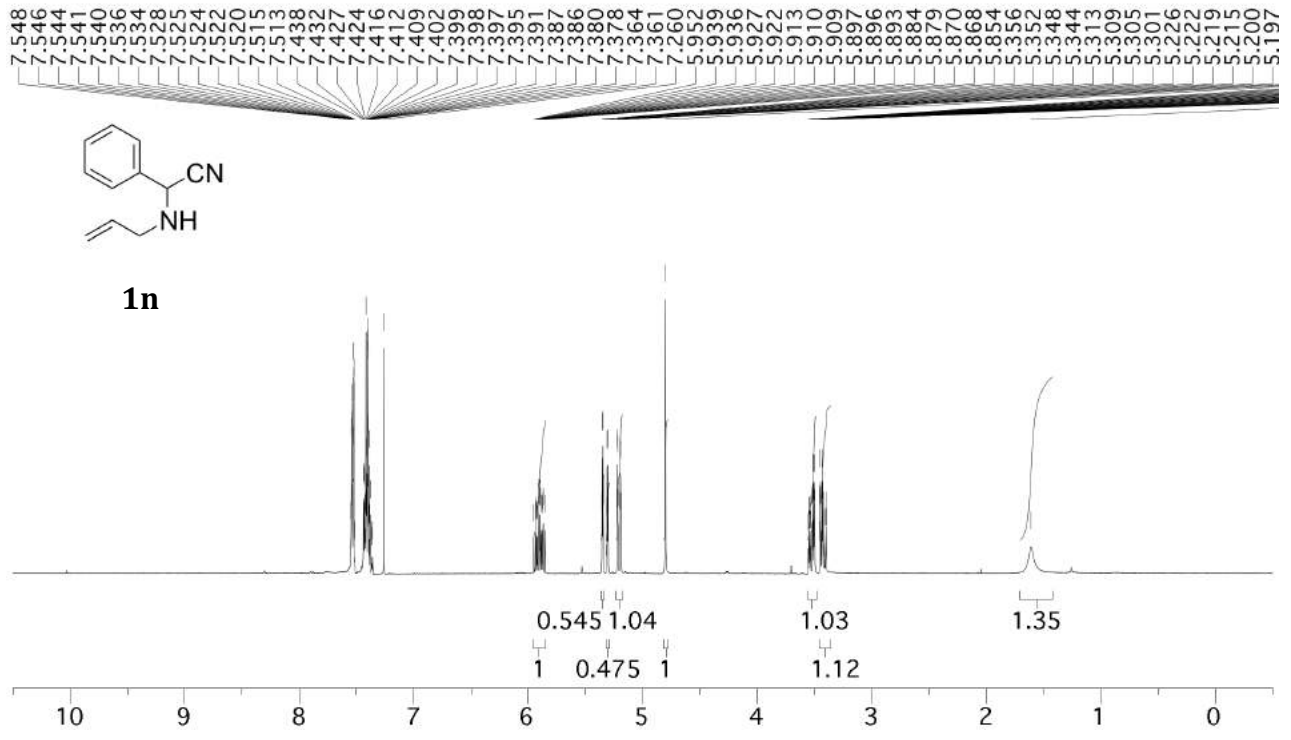


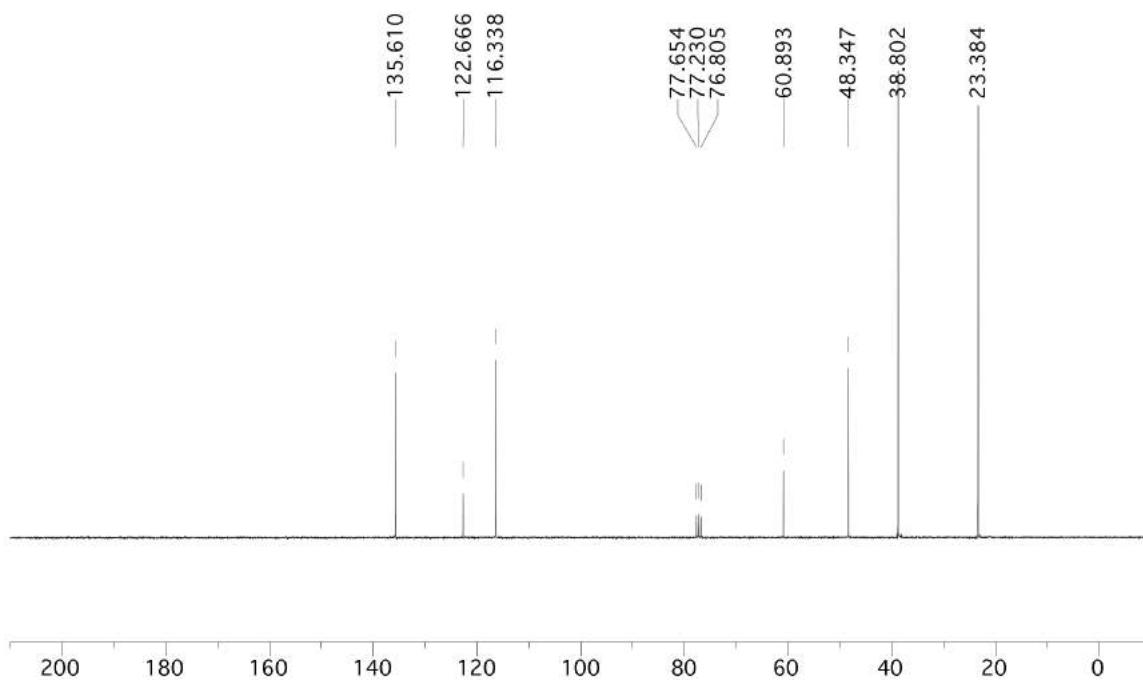
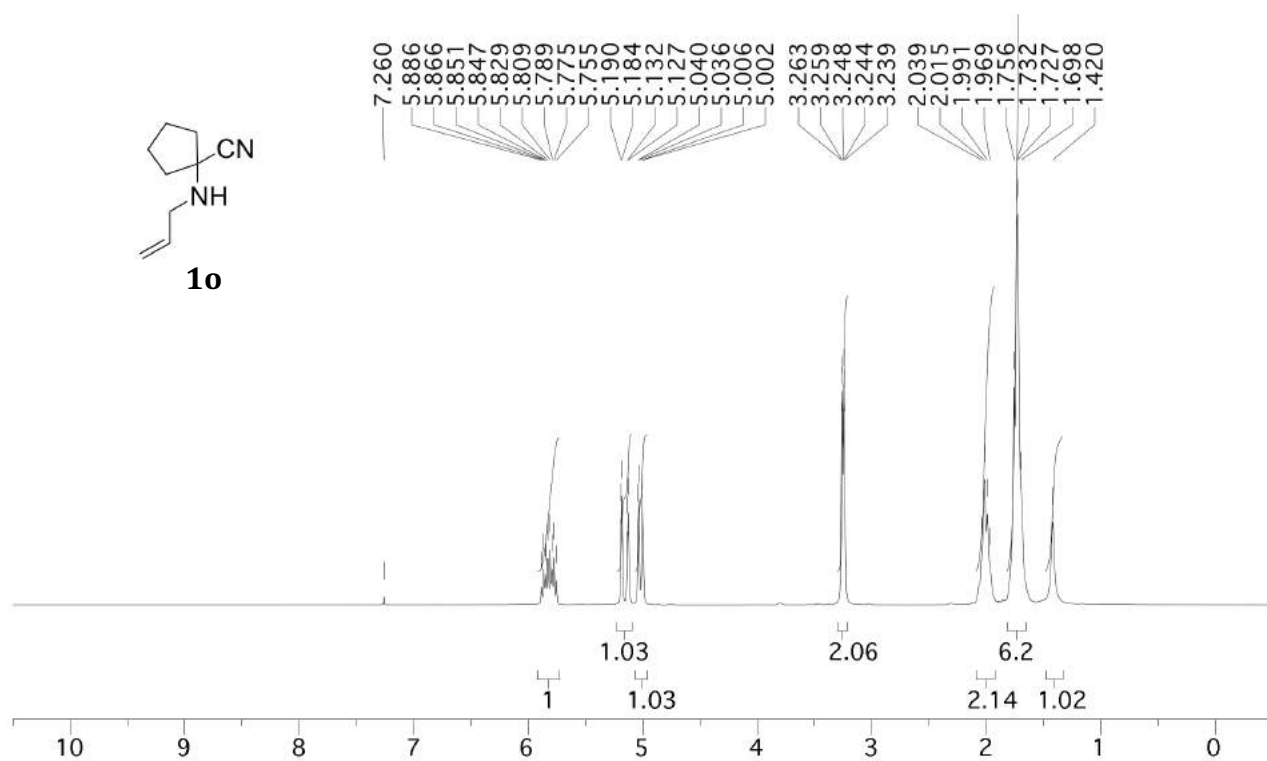
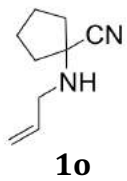


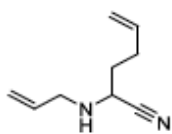




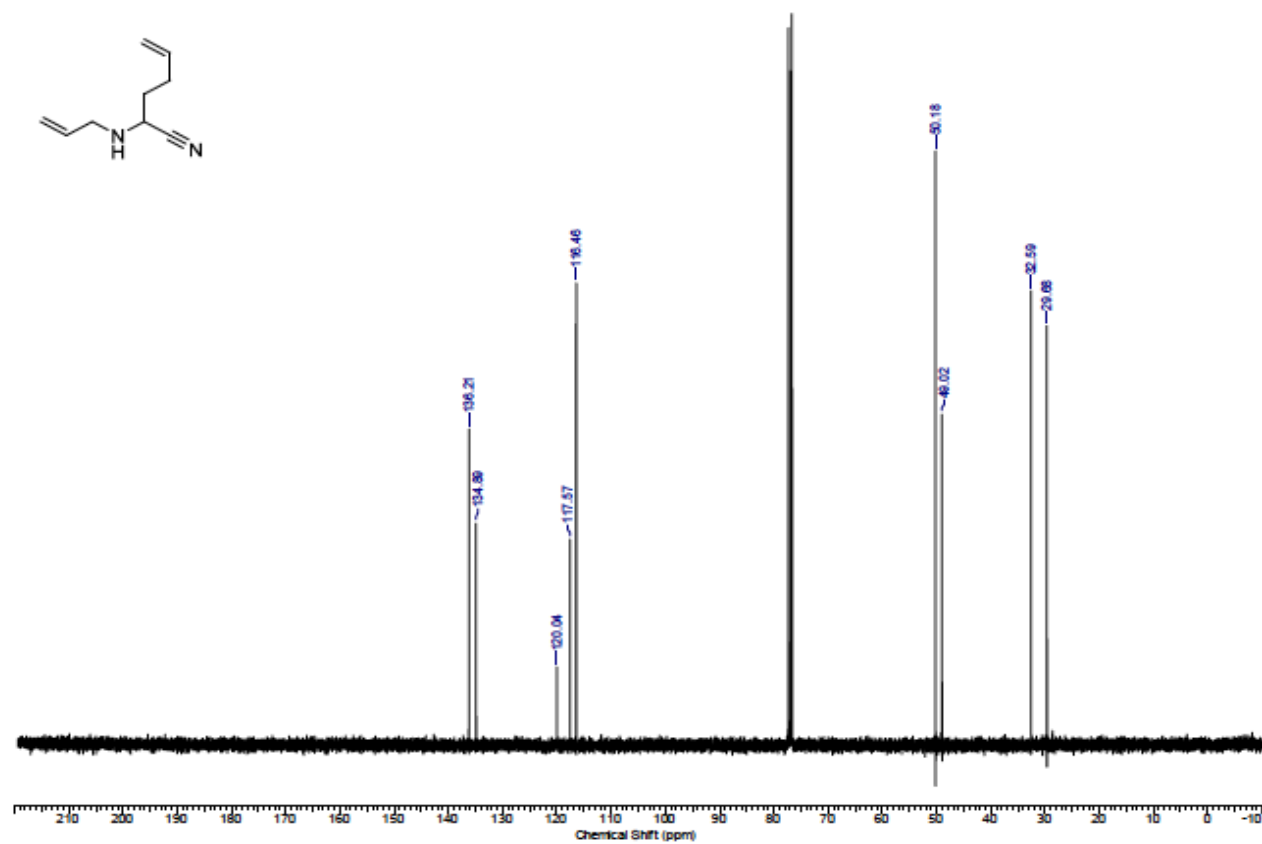
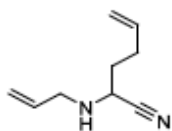
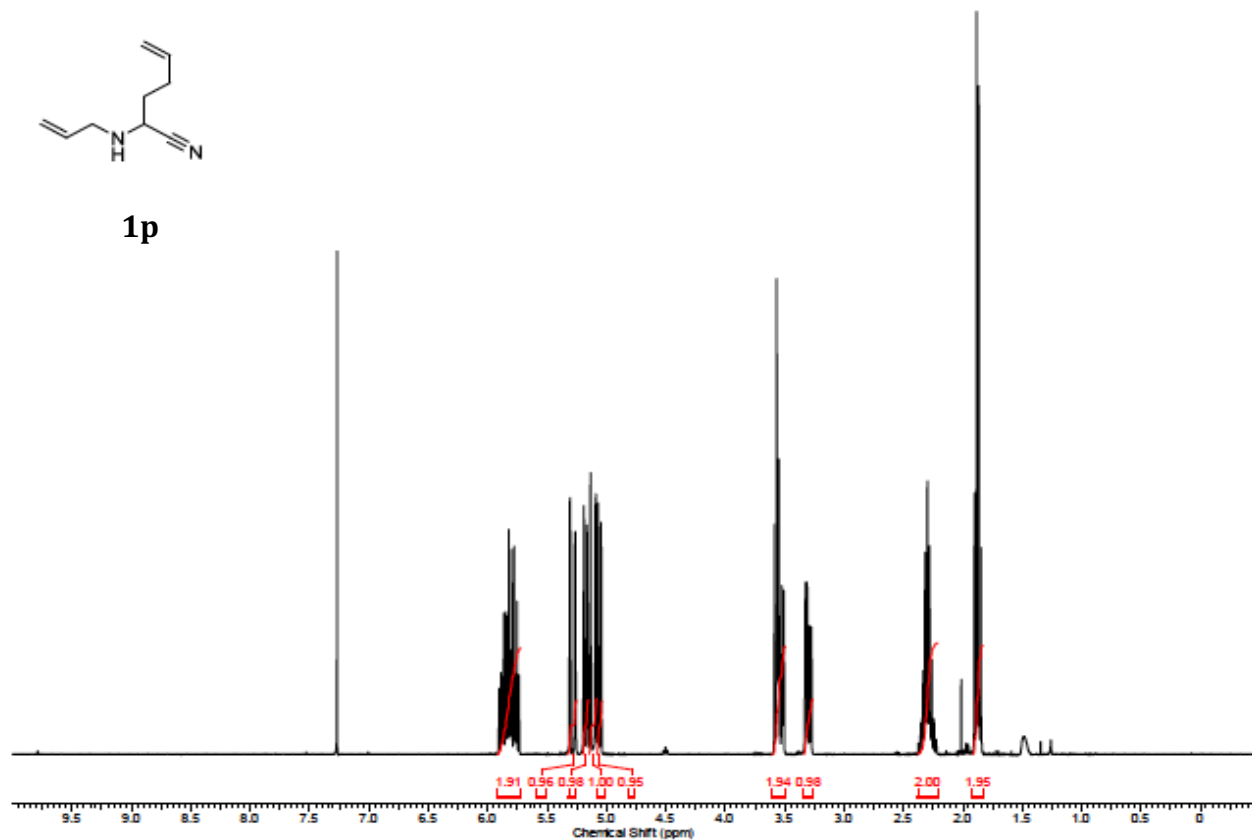




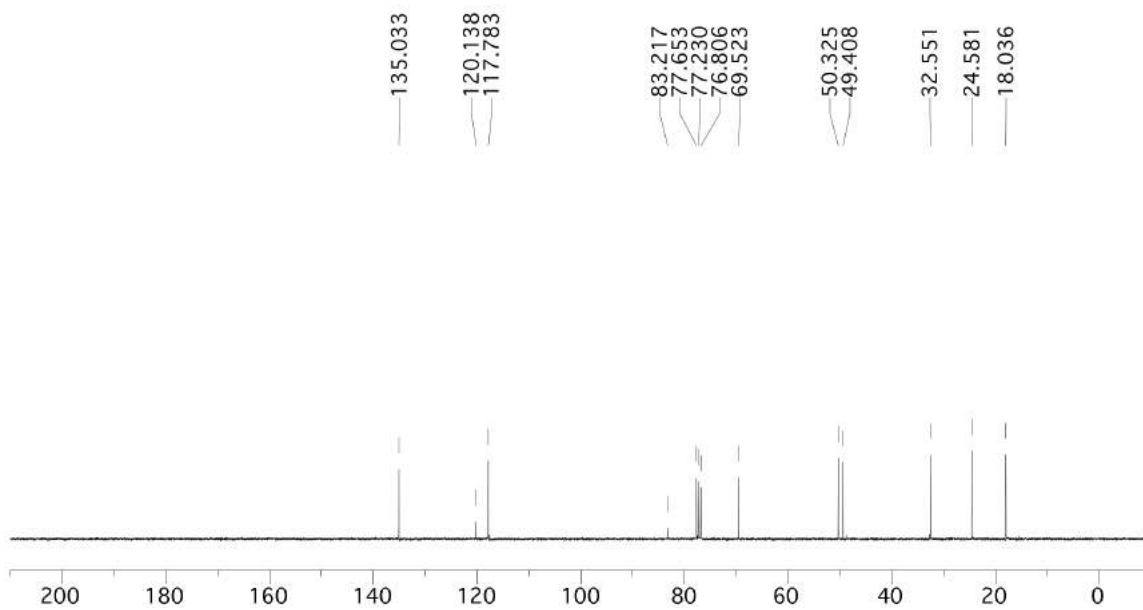
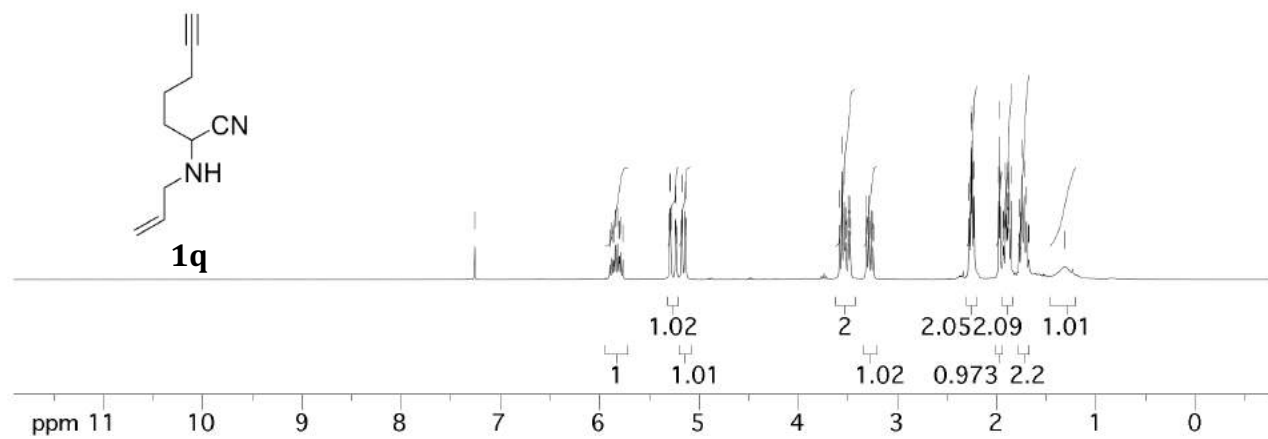


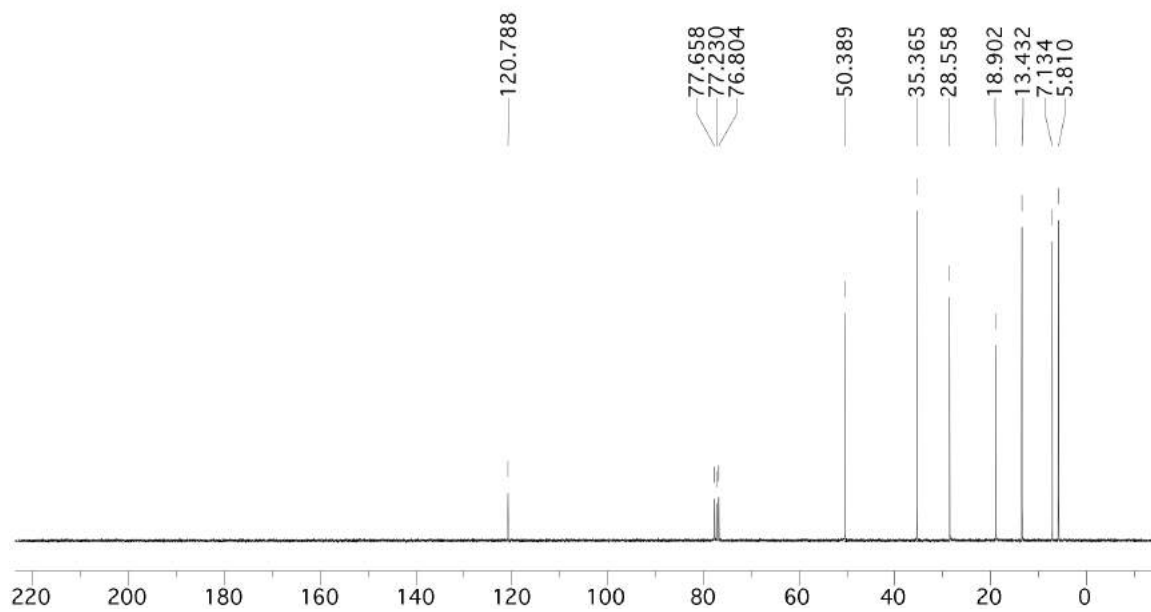
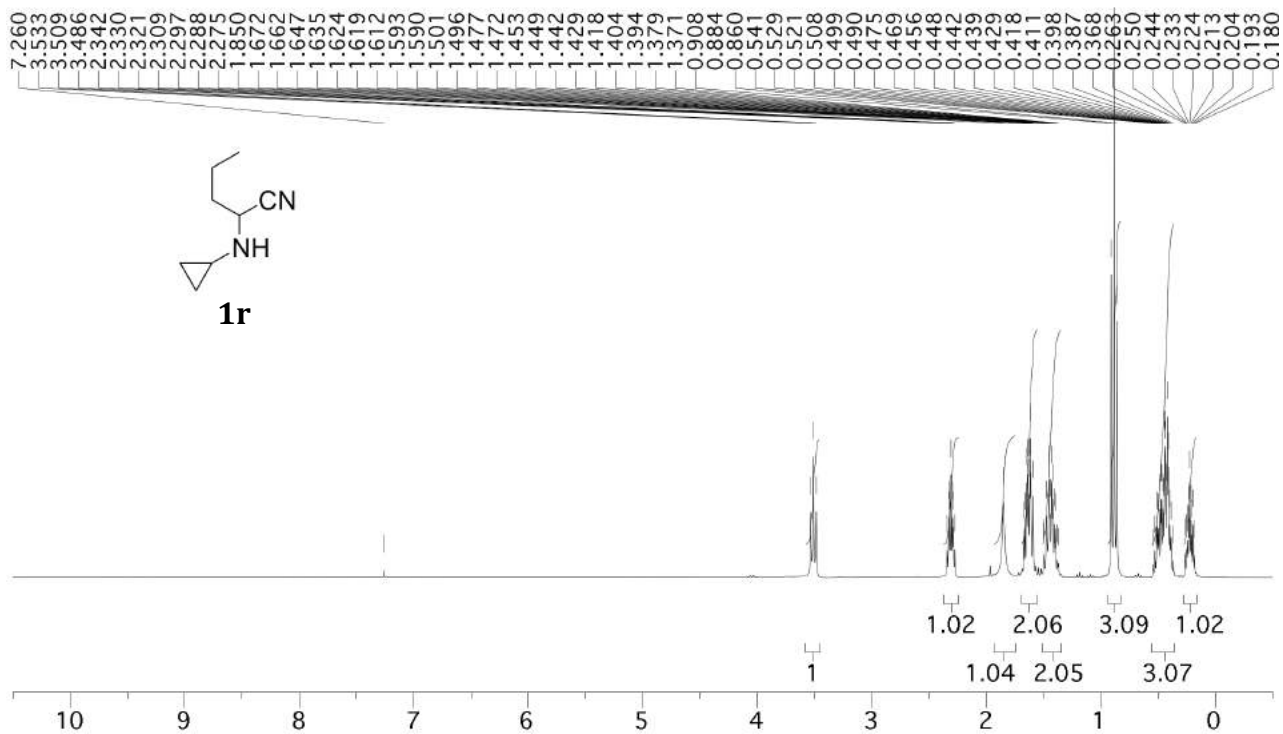


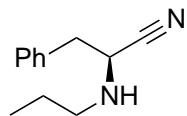
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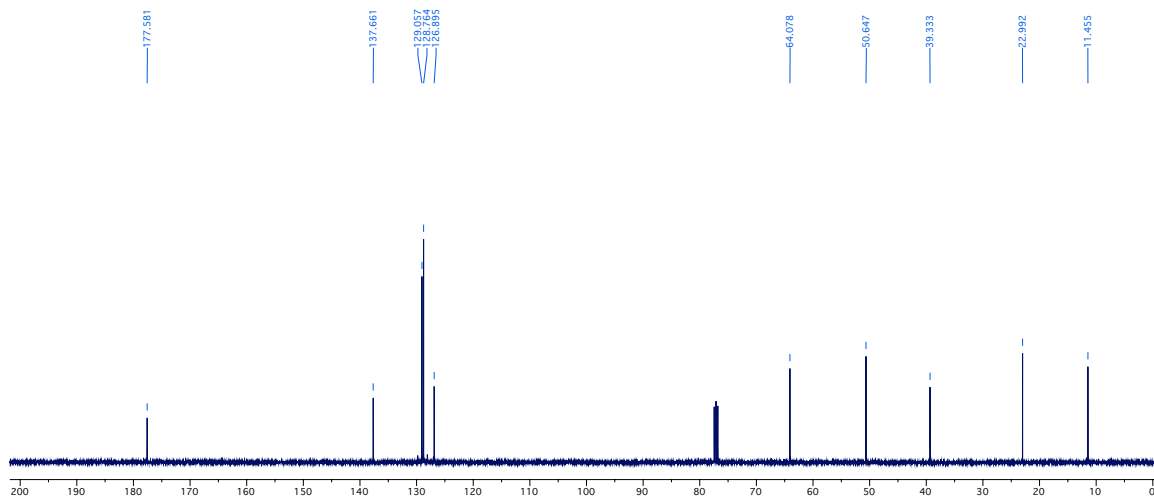
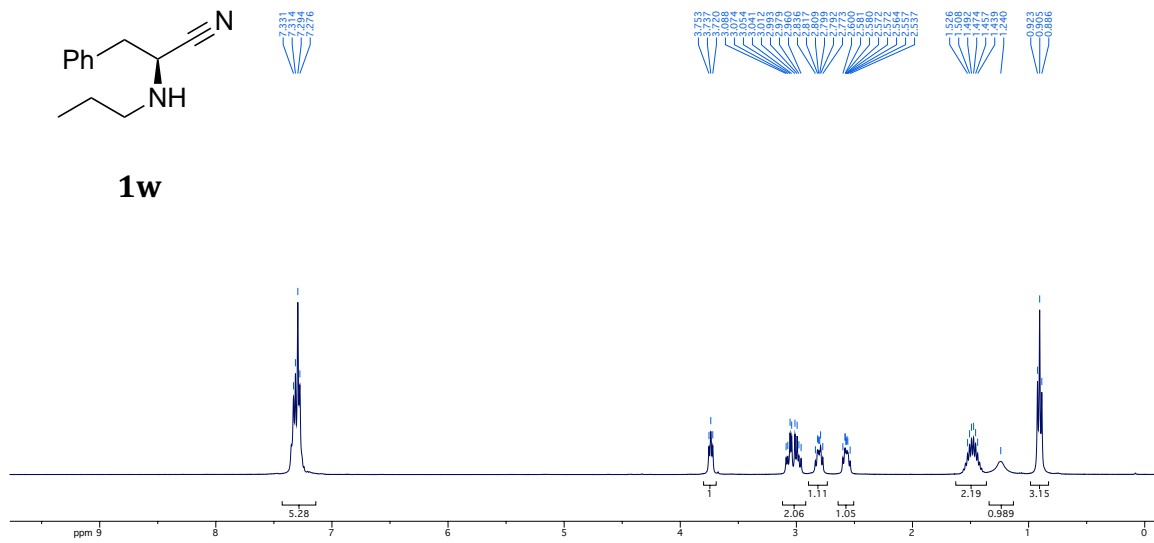
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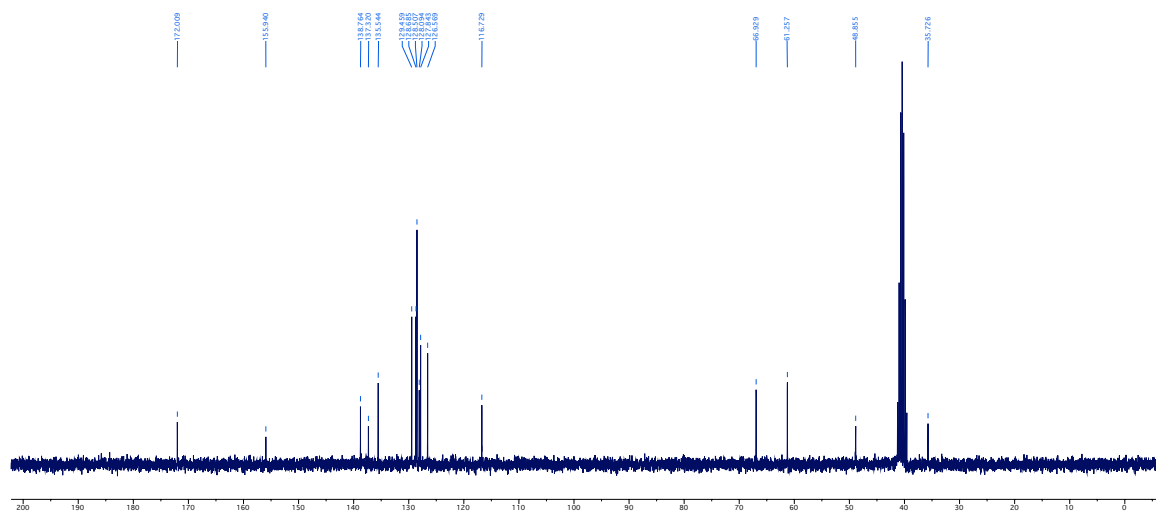
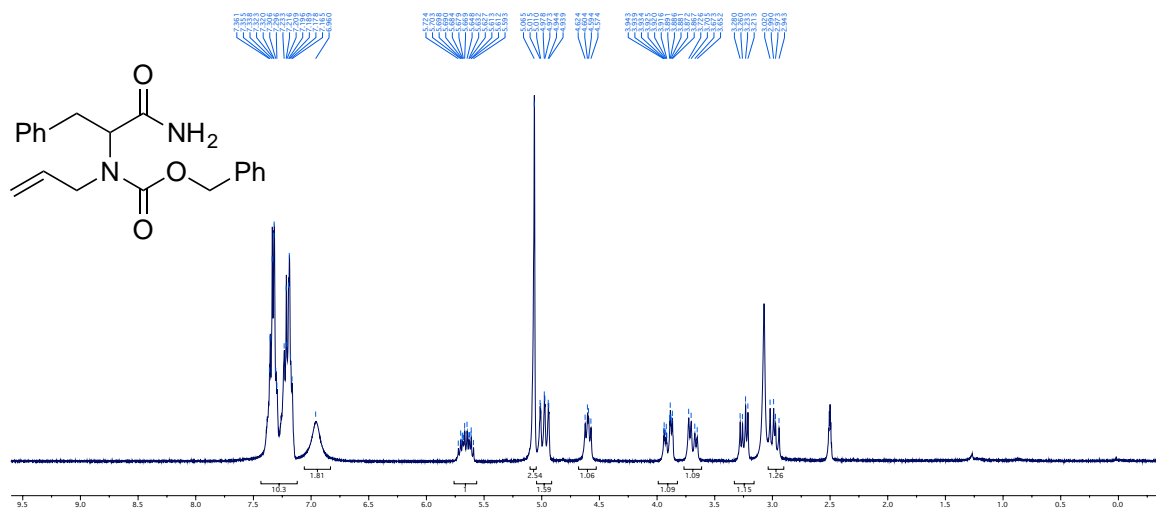


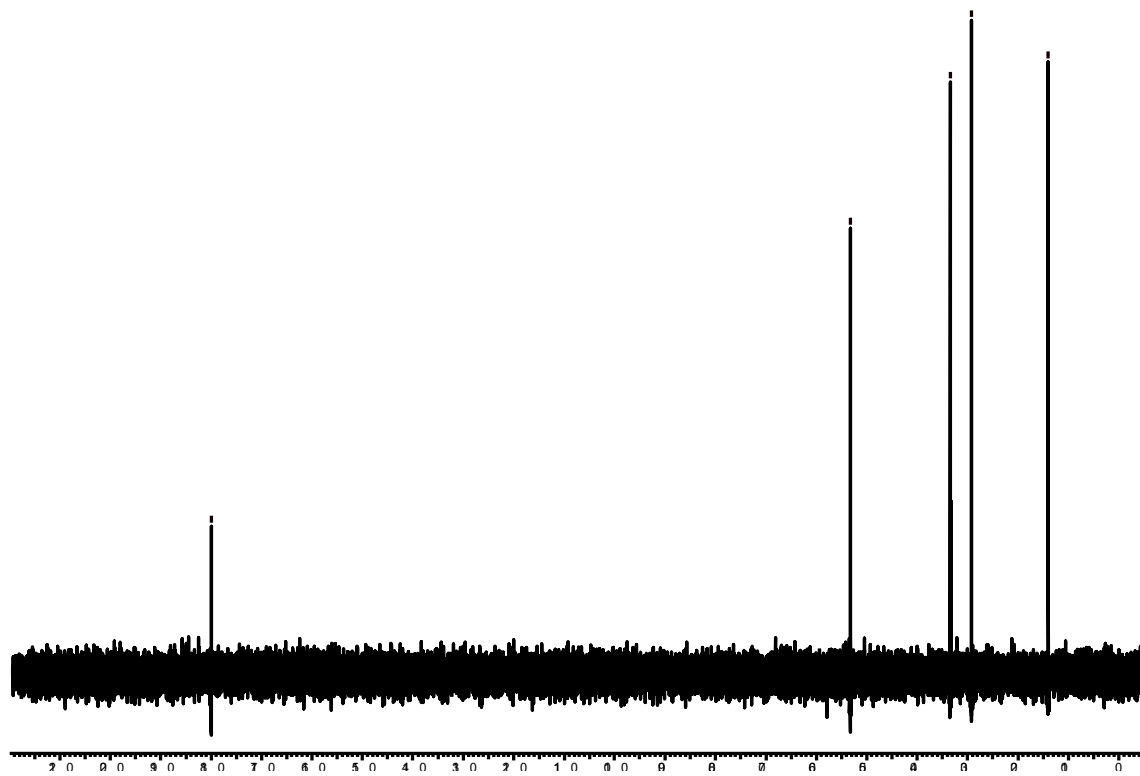
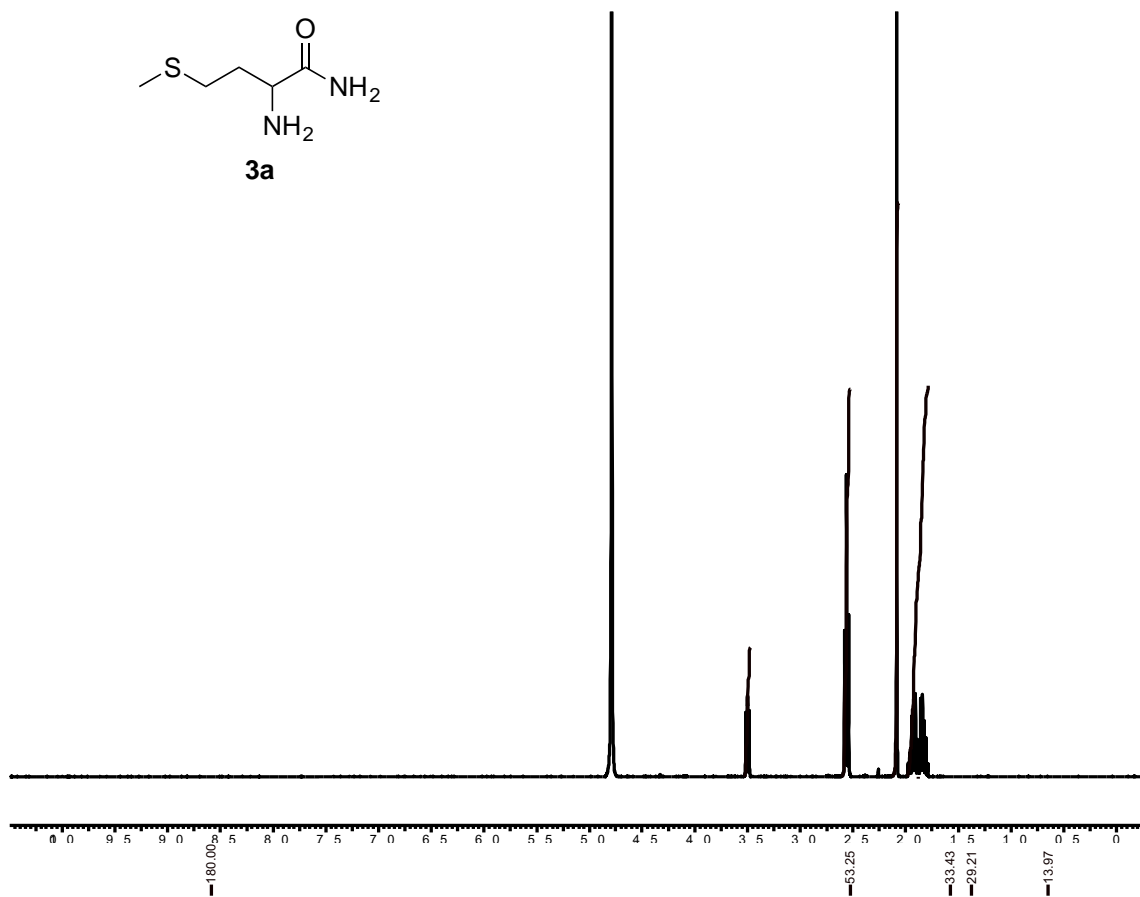
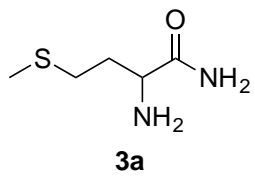
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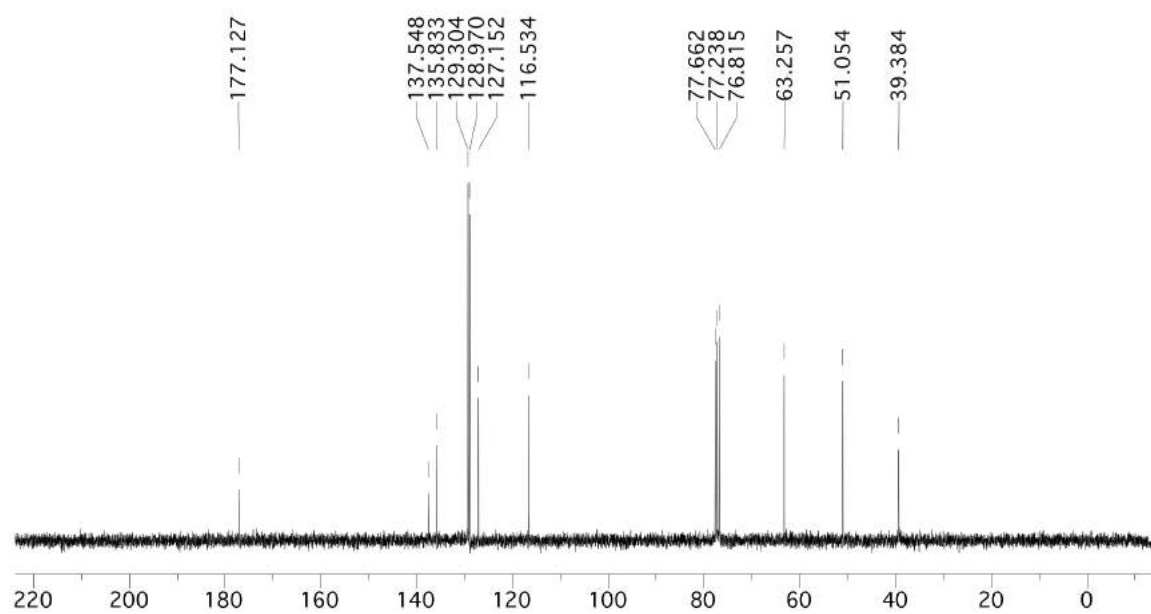
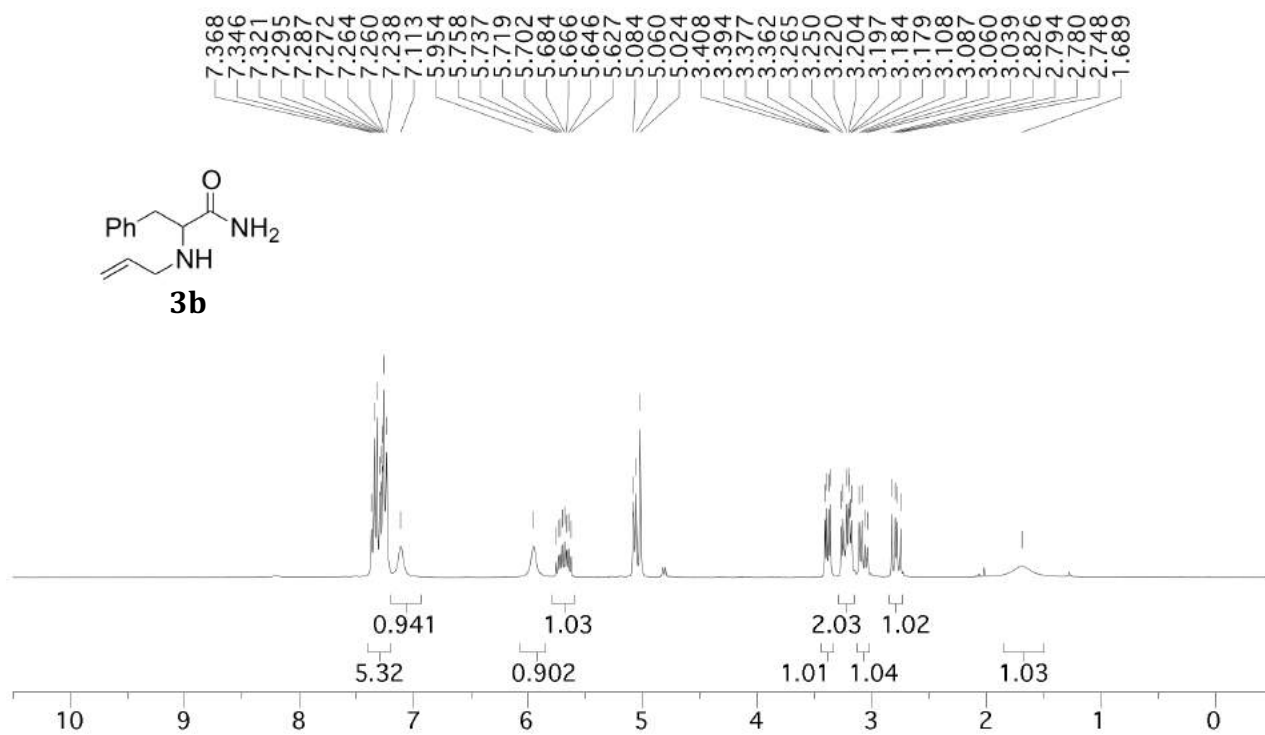


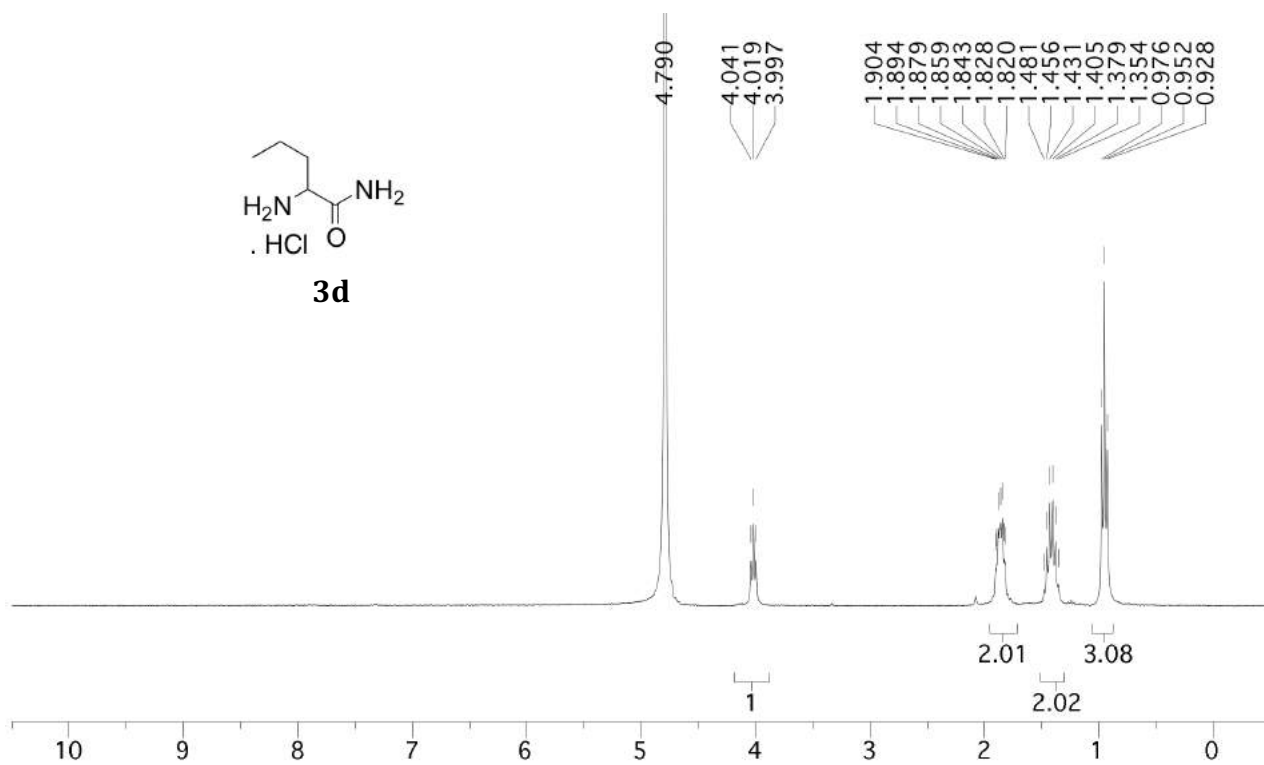
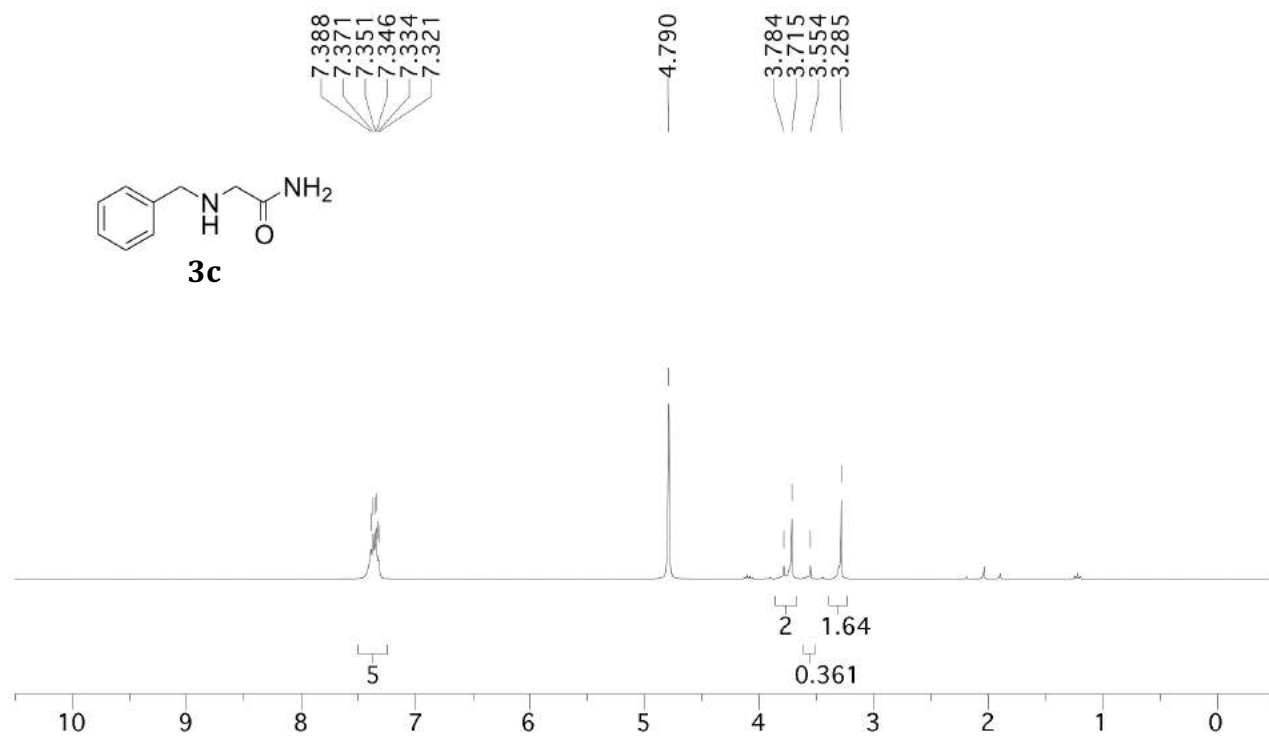


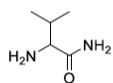




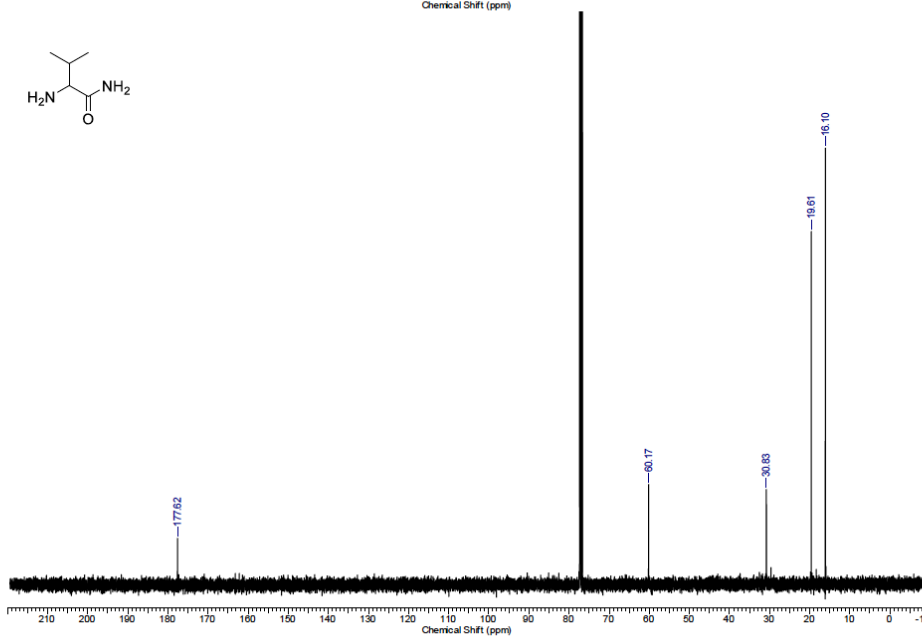
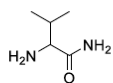
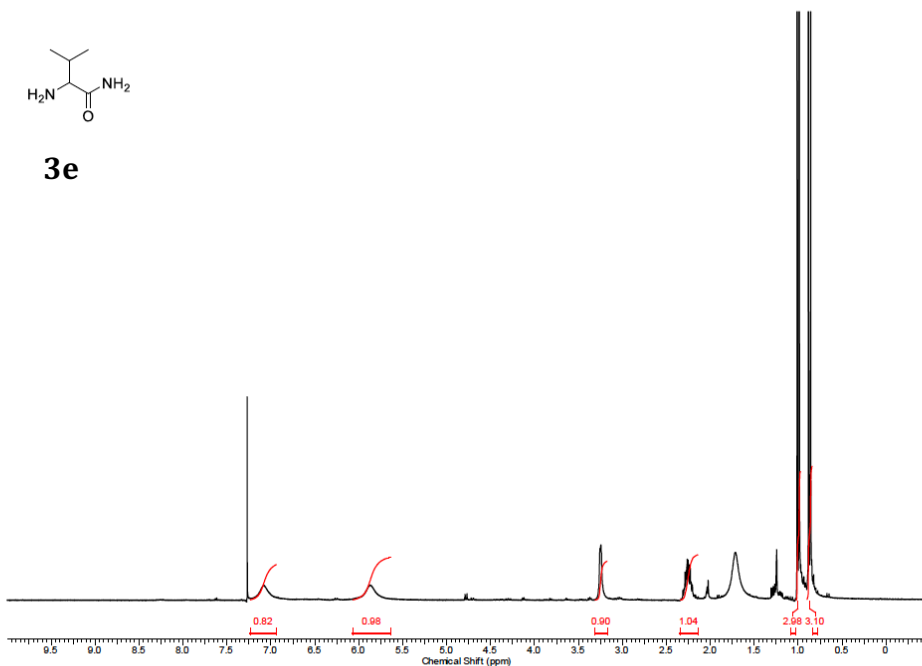


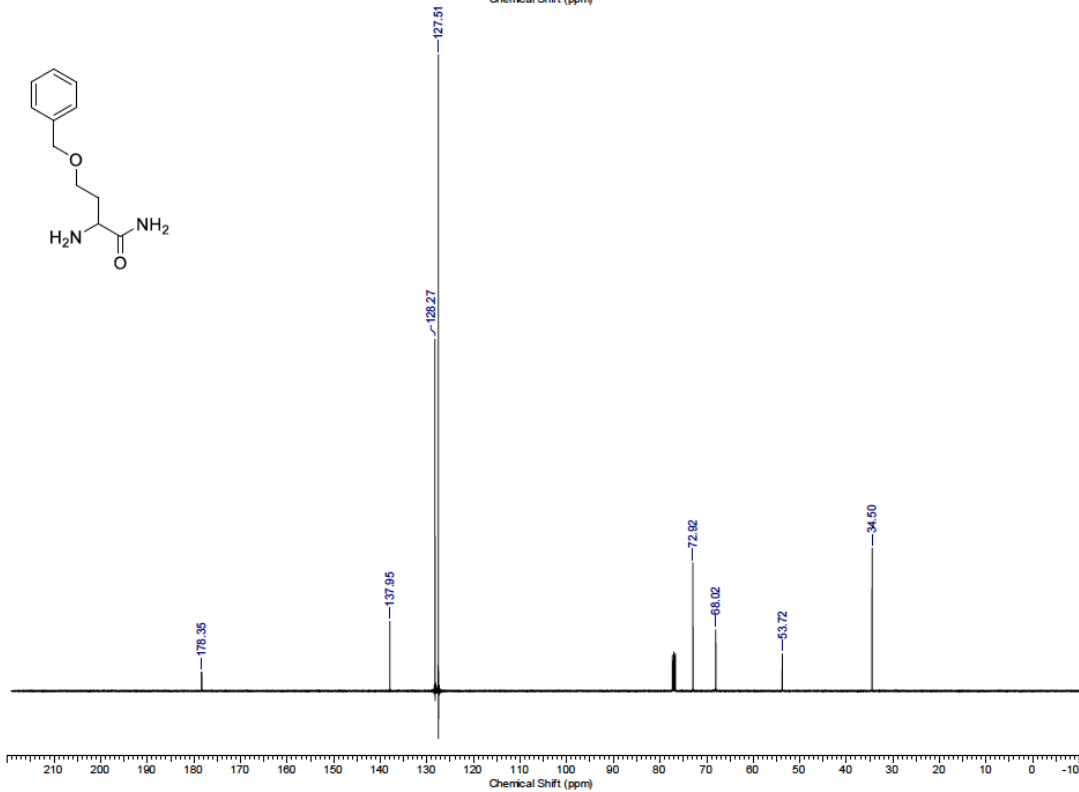
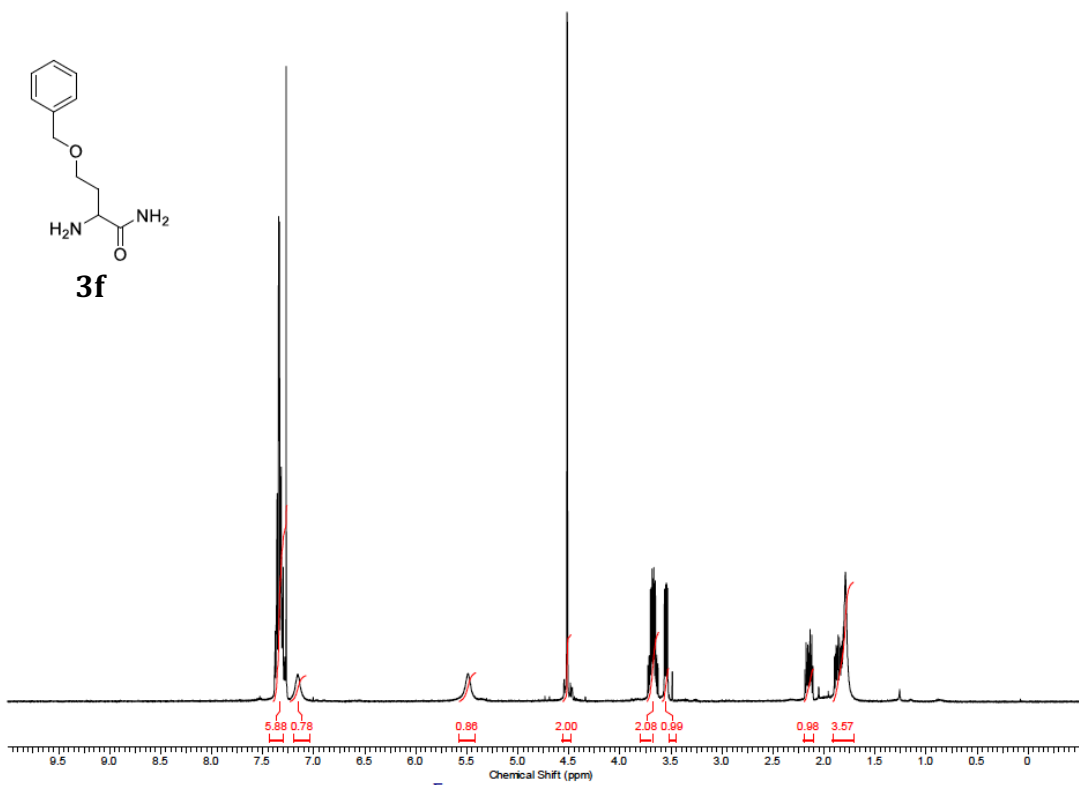


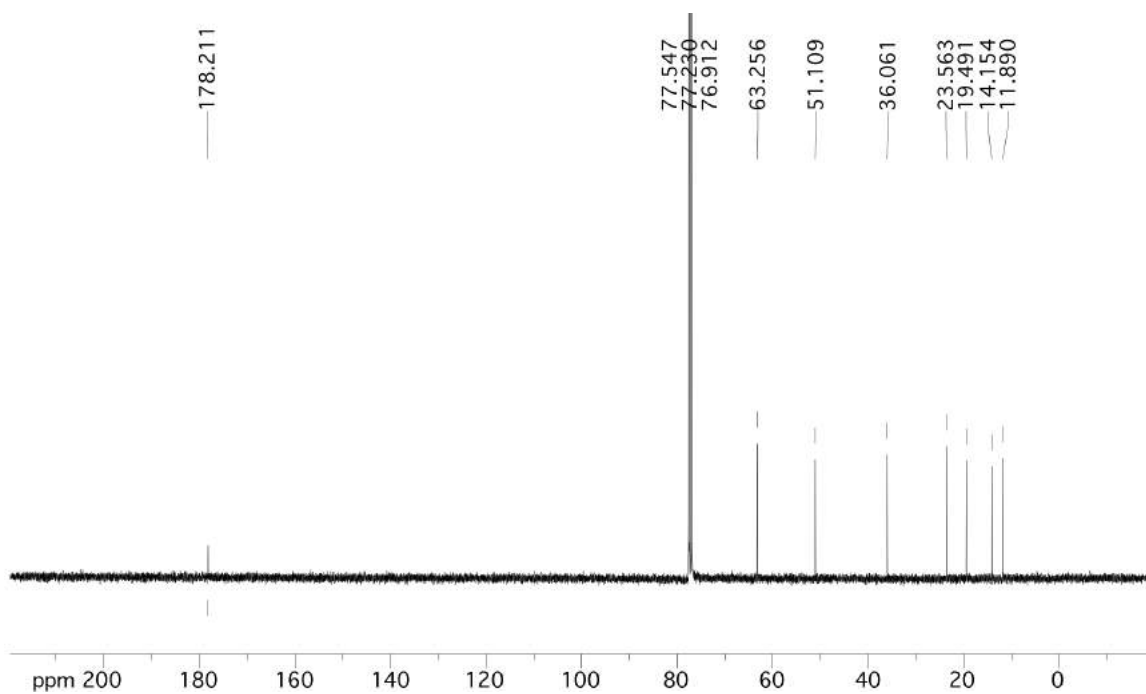
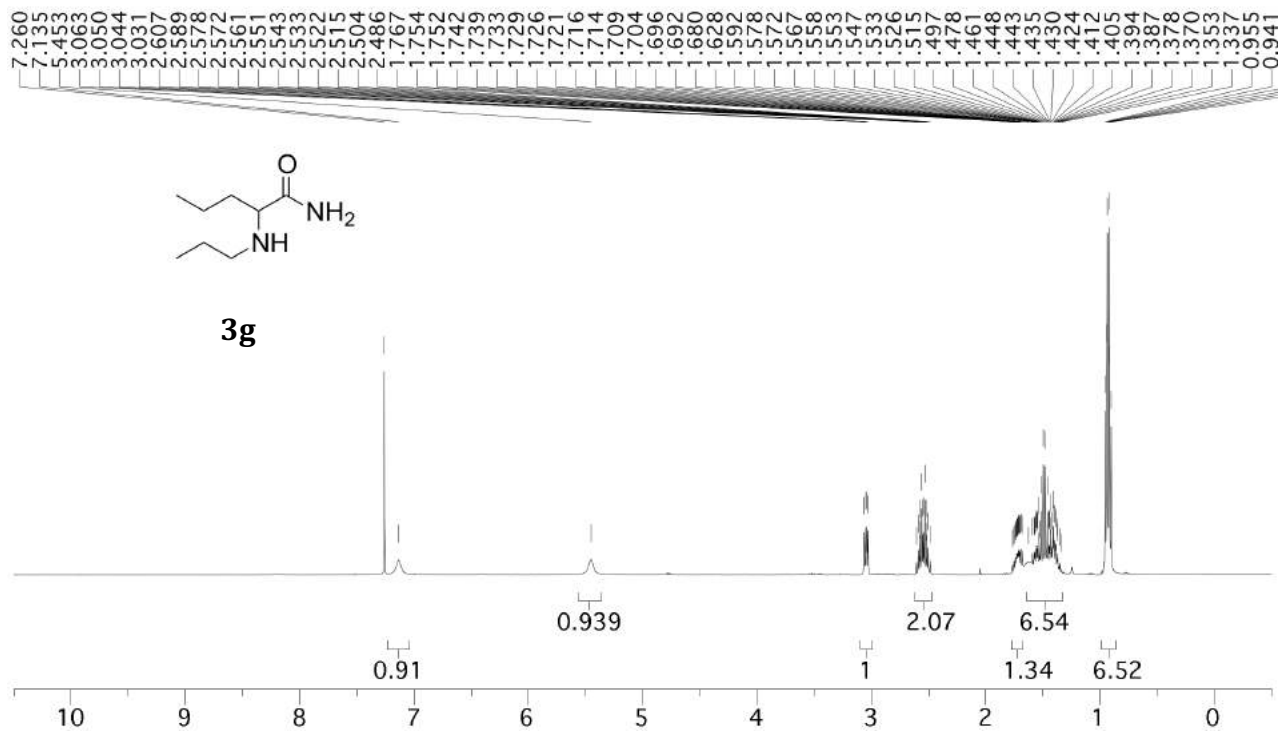




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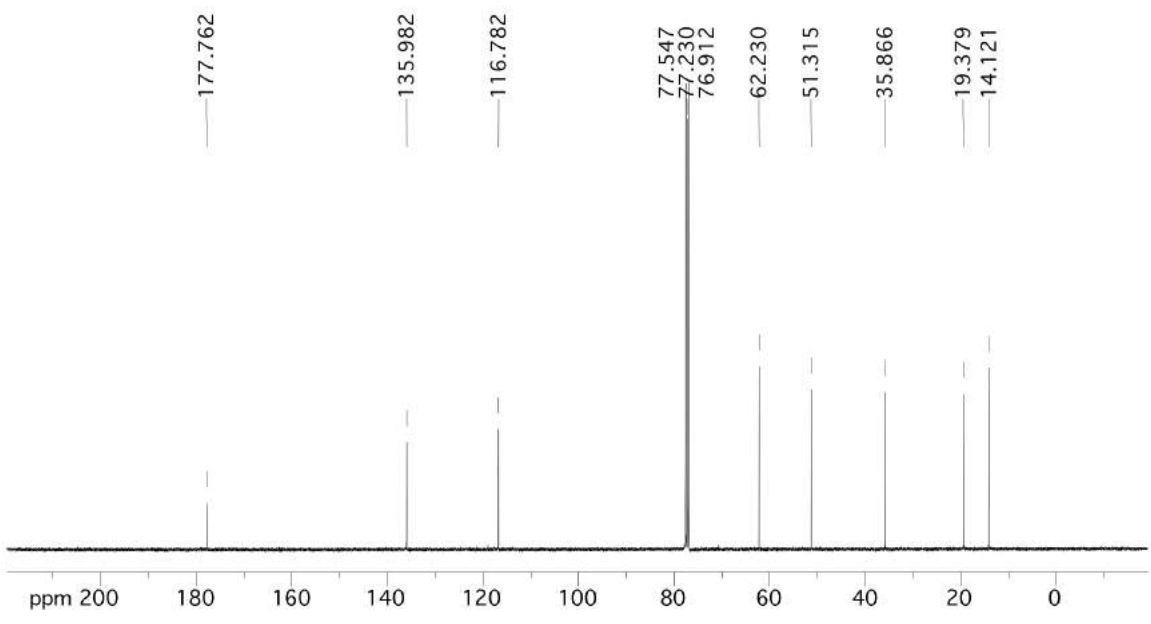
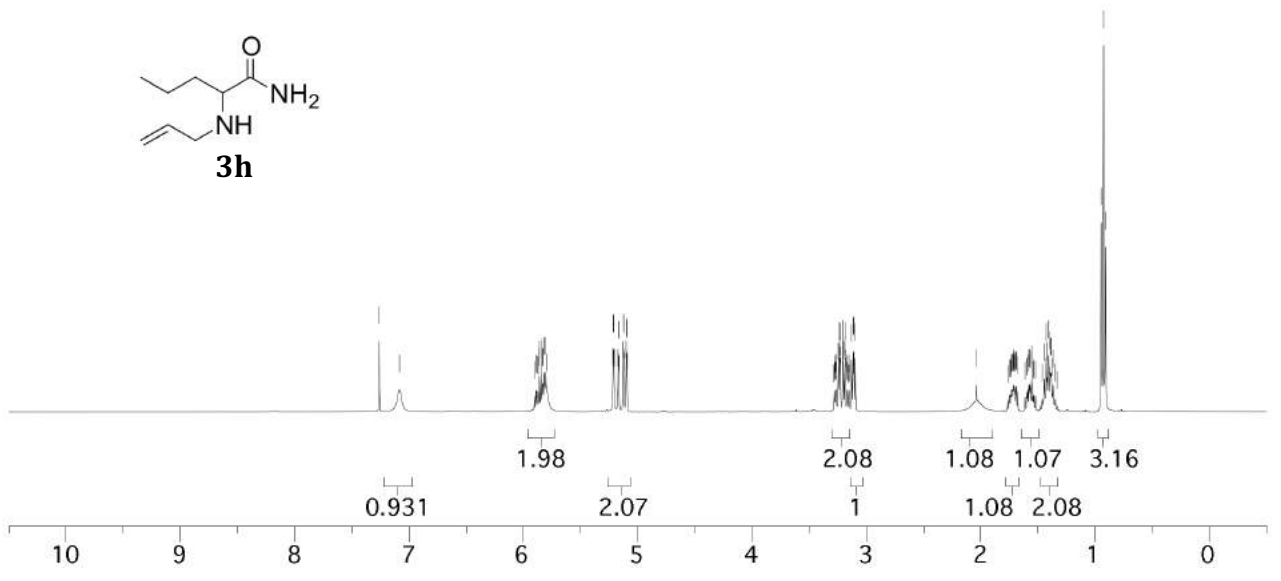
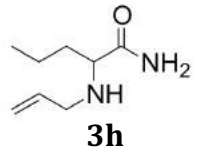


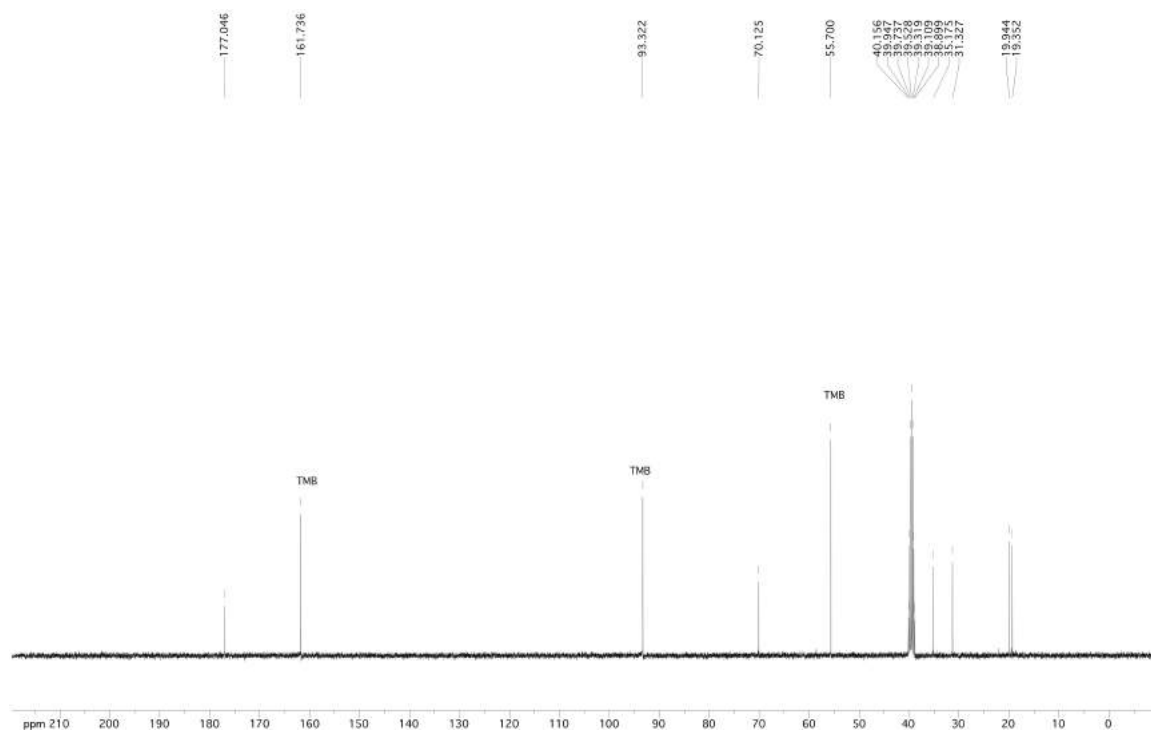
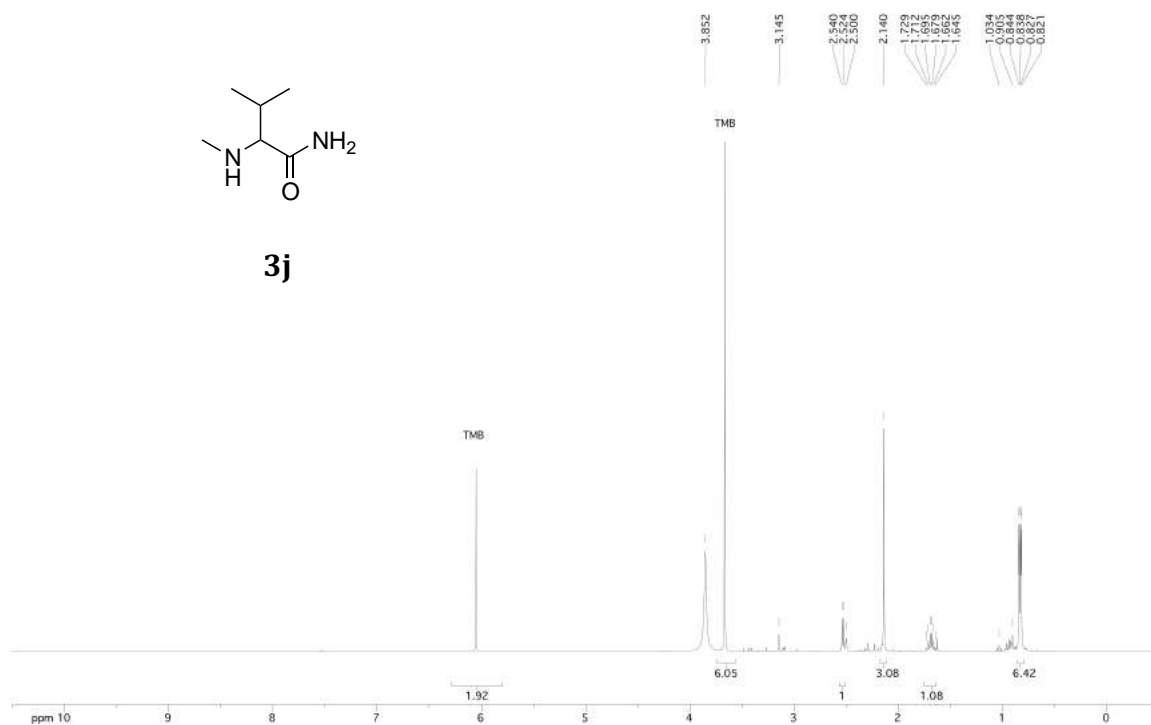
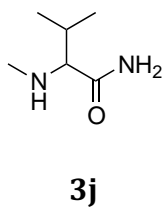


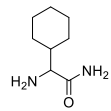




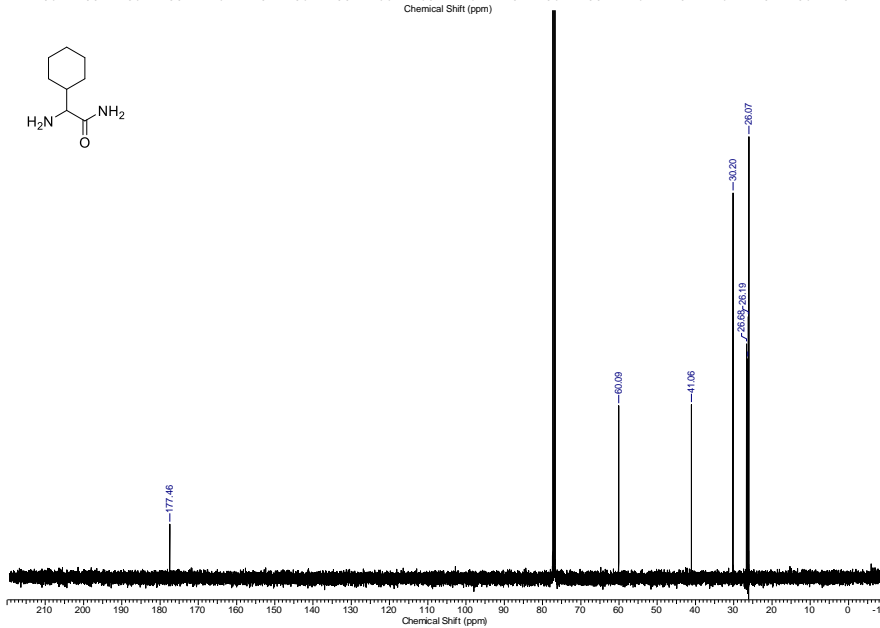
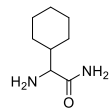
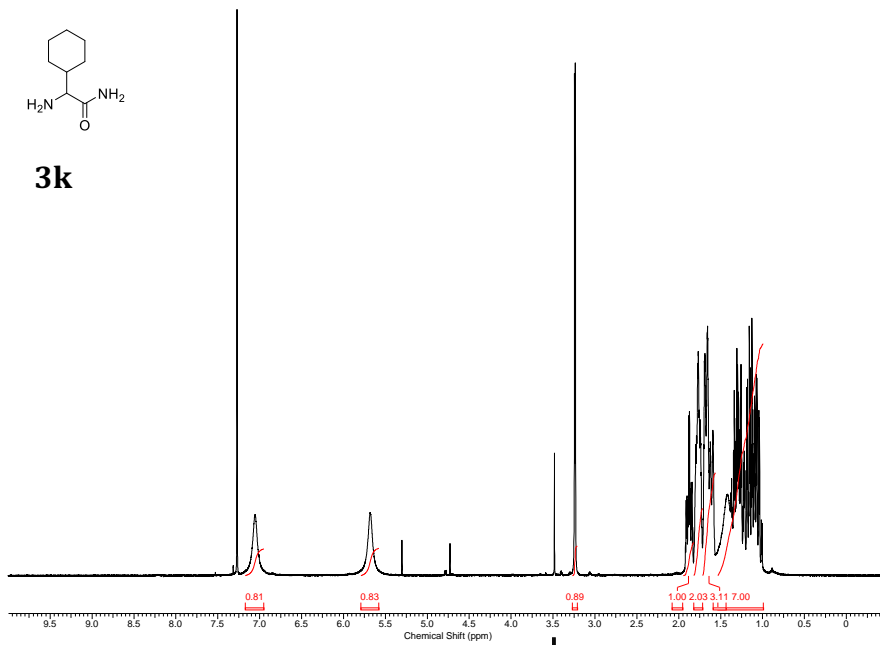
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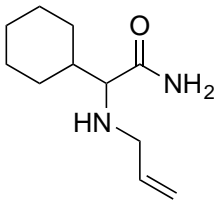




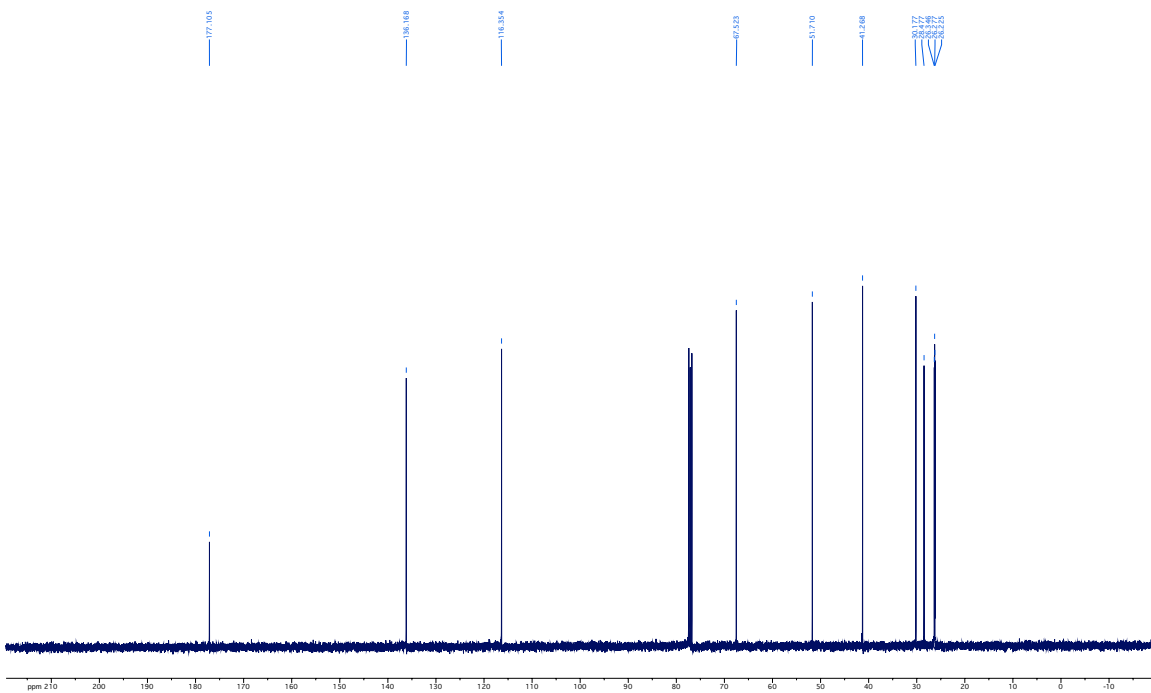
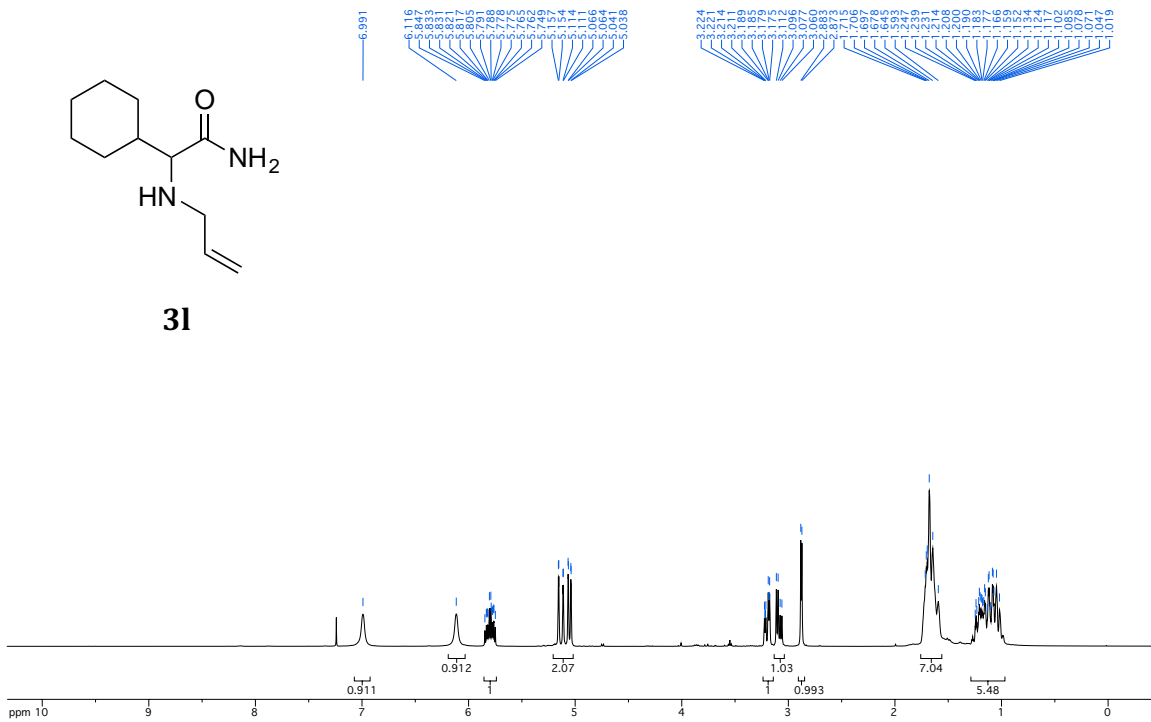


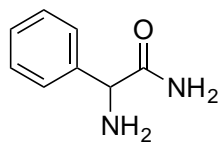
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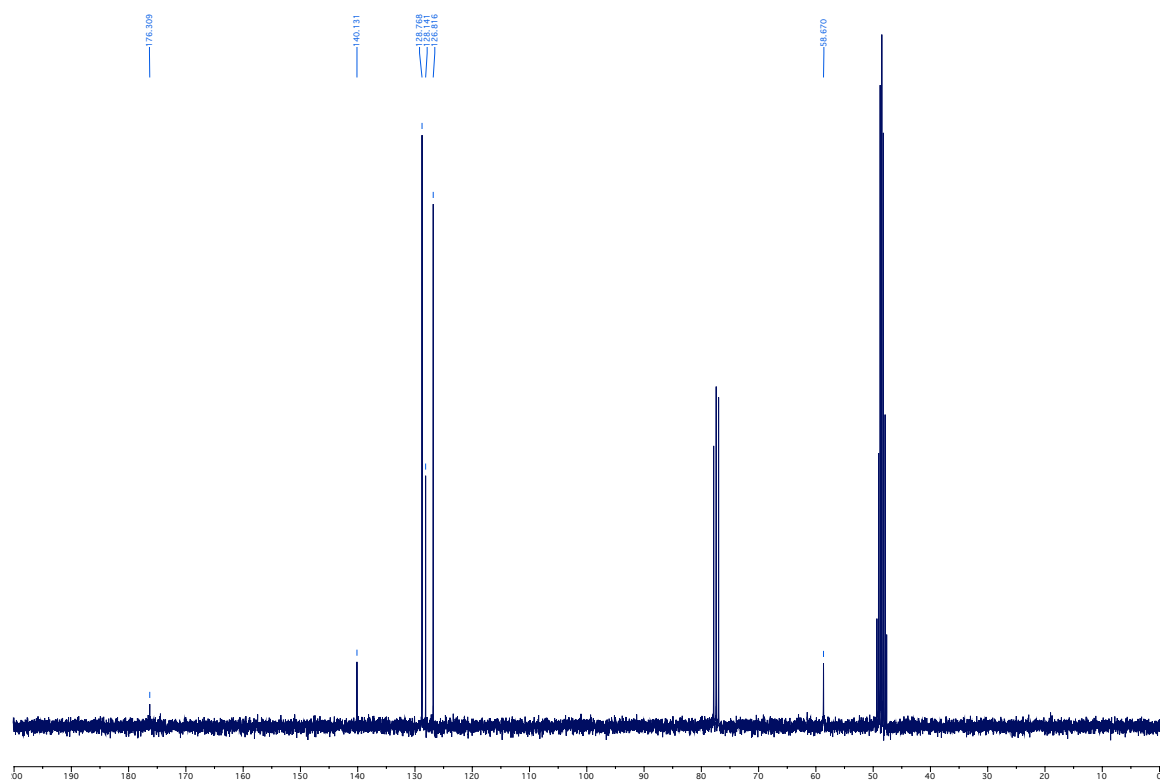
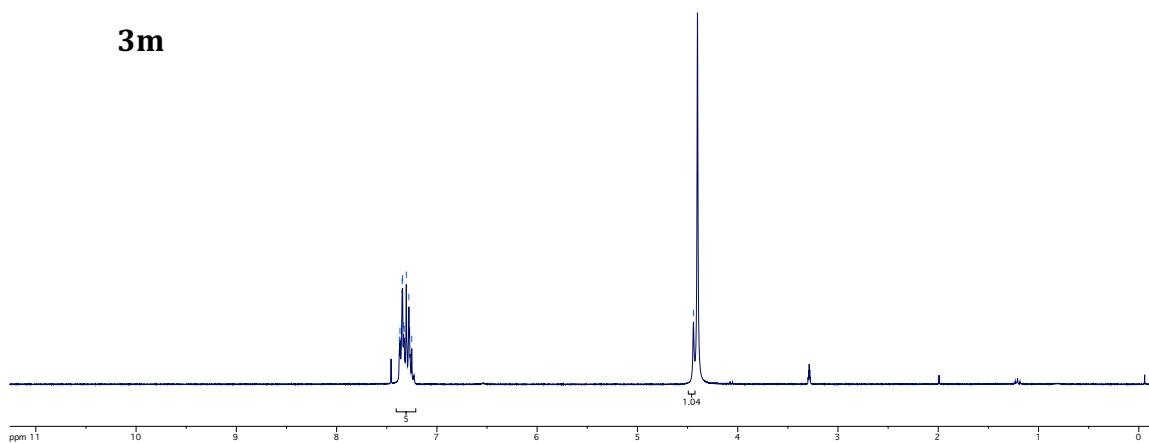


31

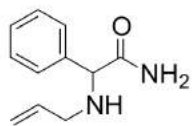




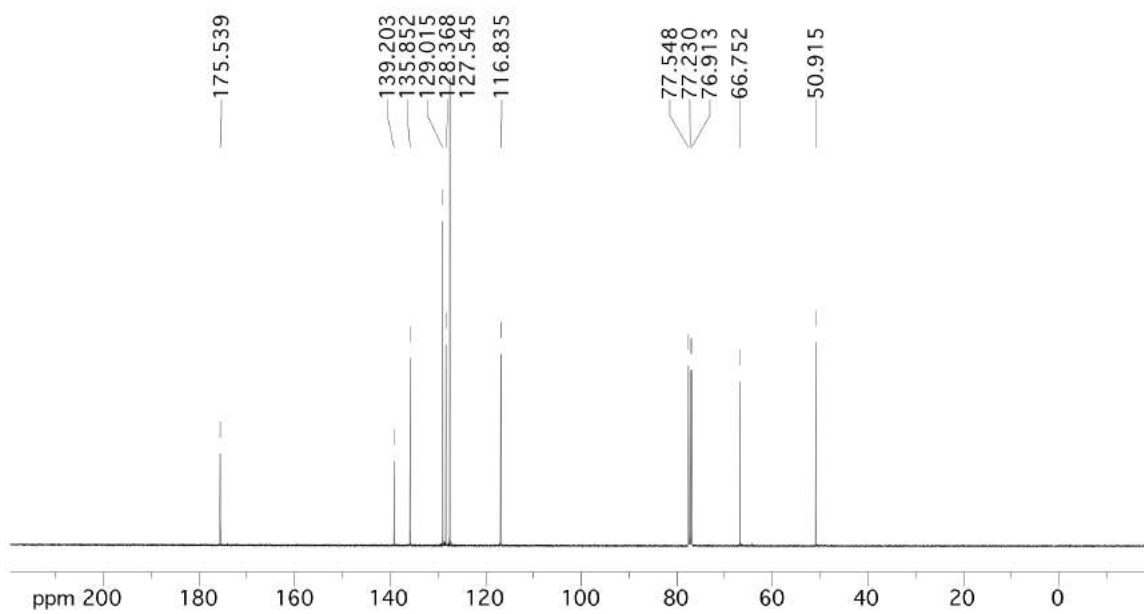
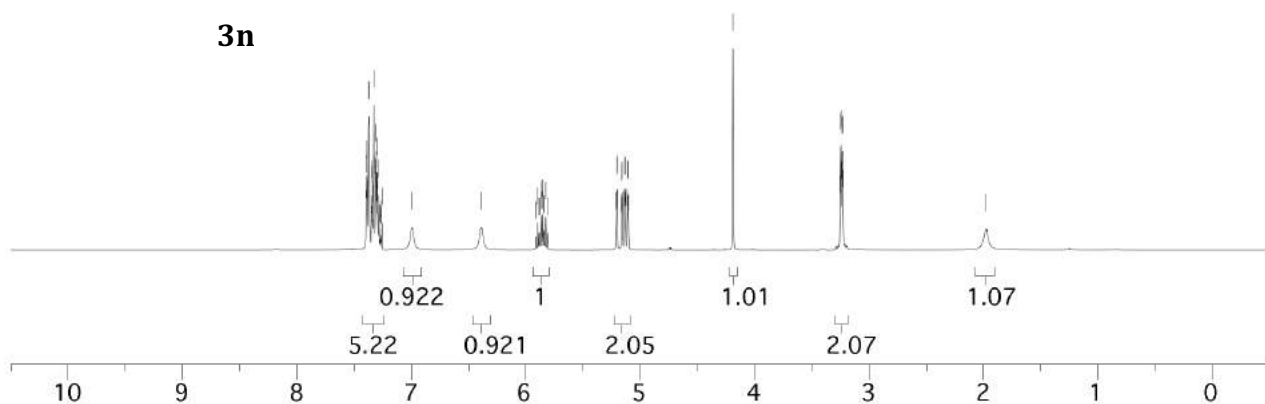
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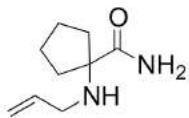
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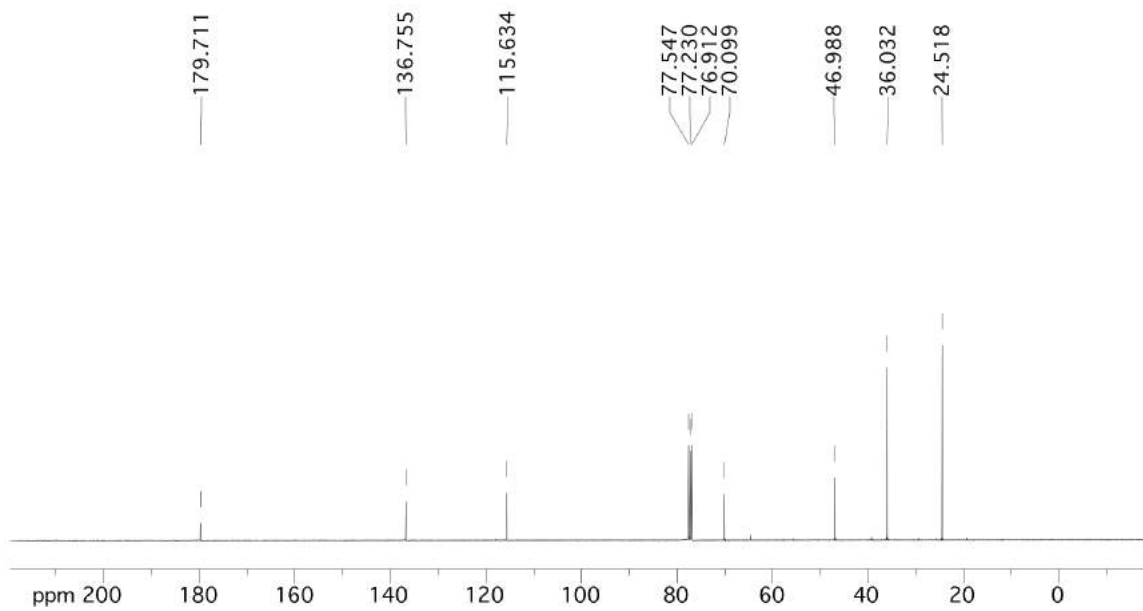
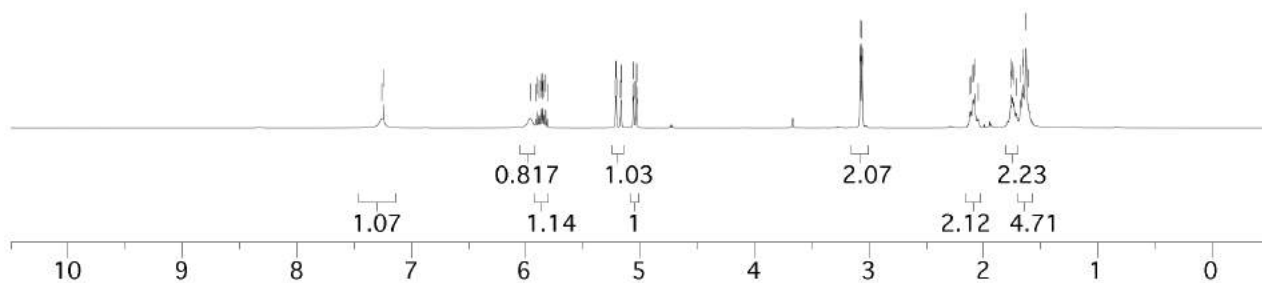
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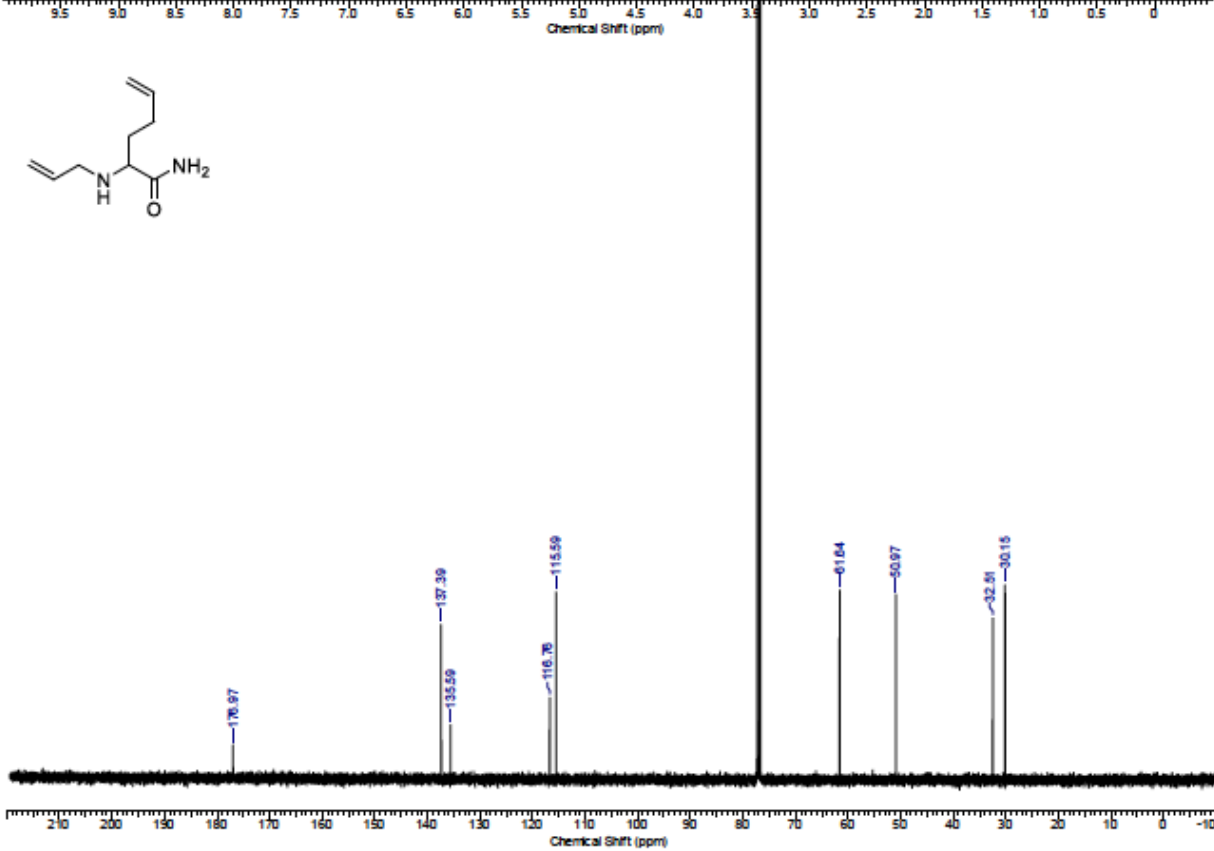
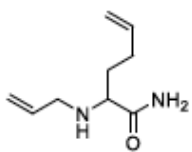
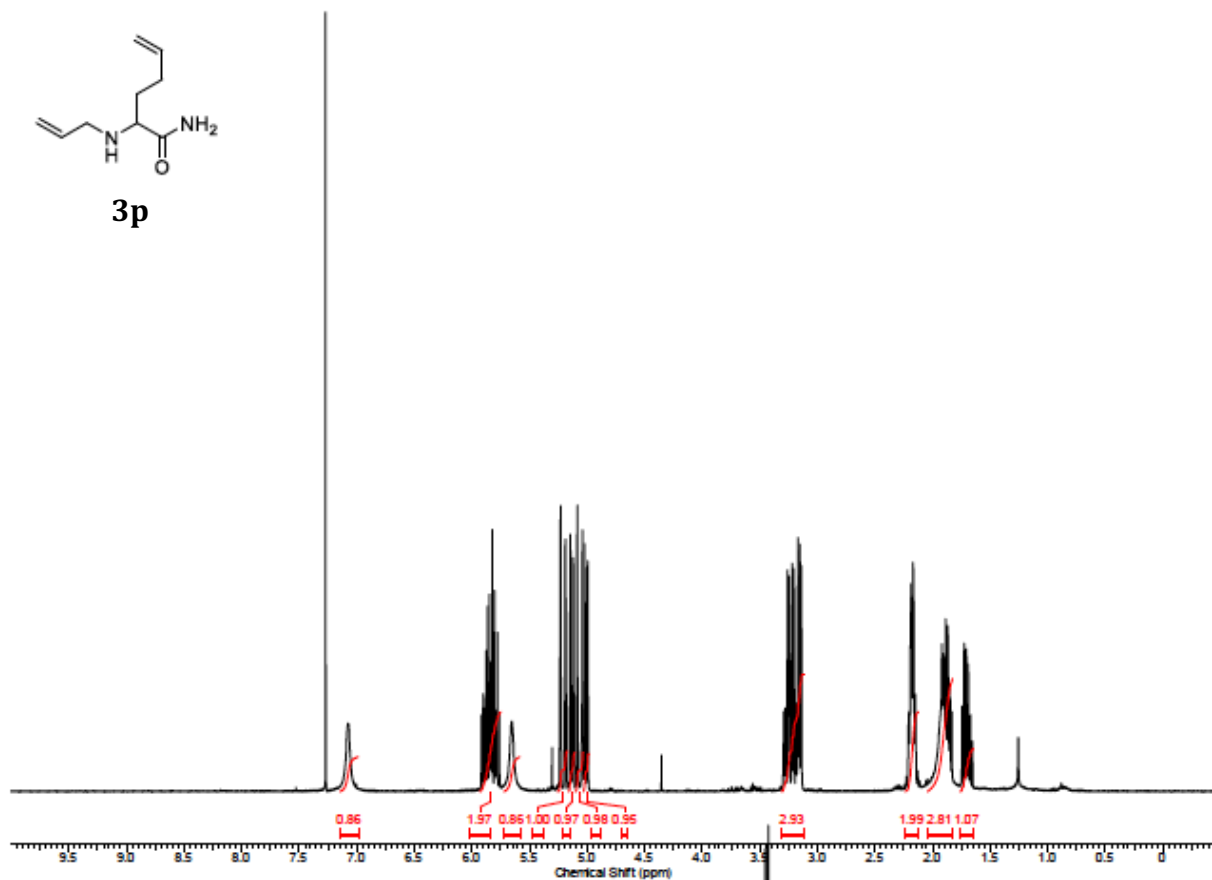
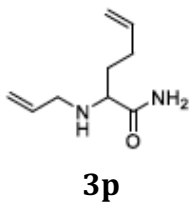


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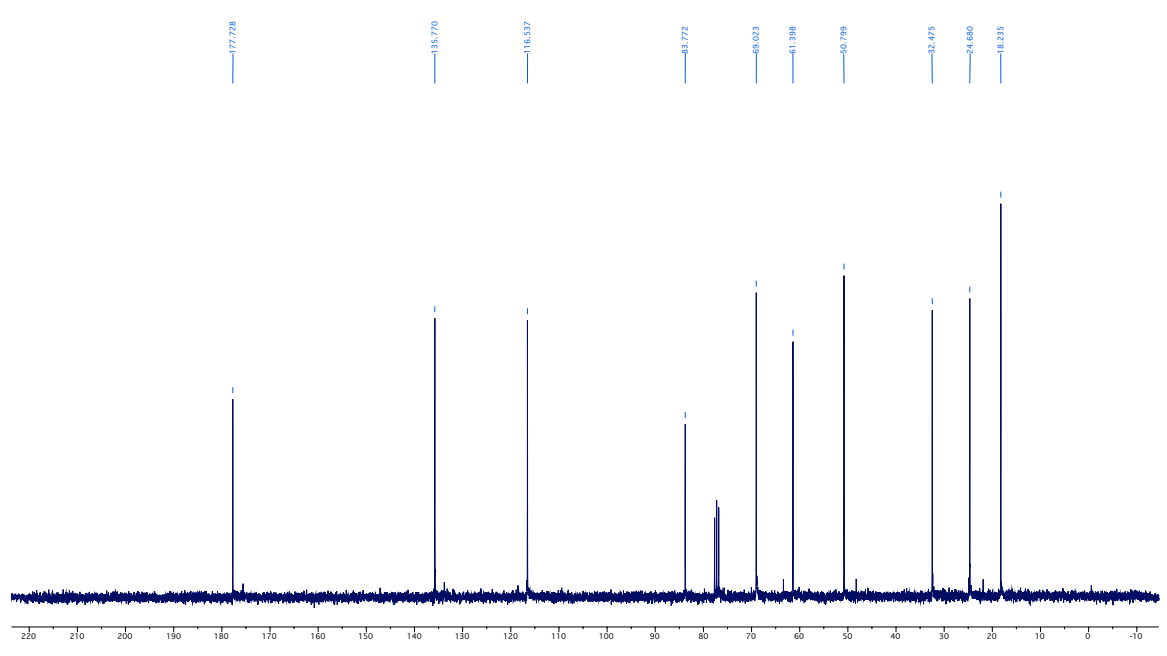
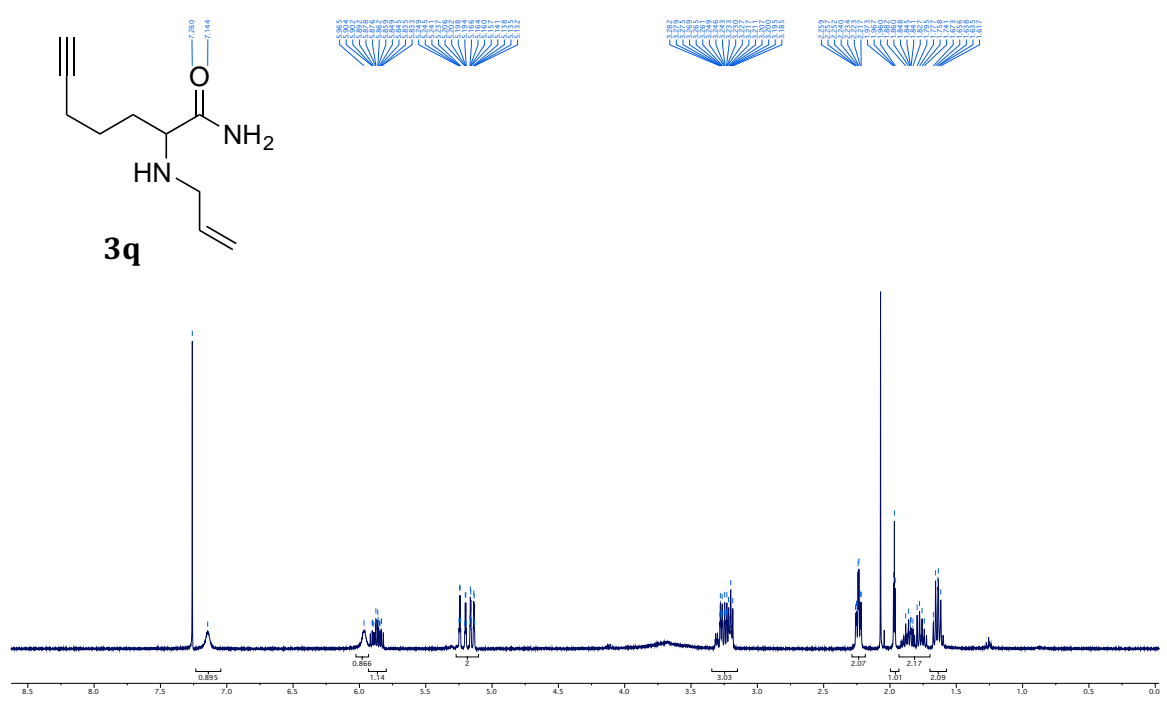
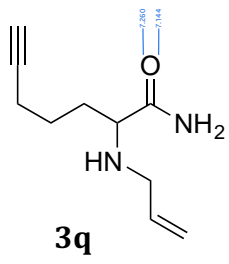


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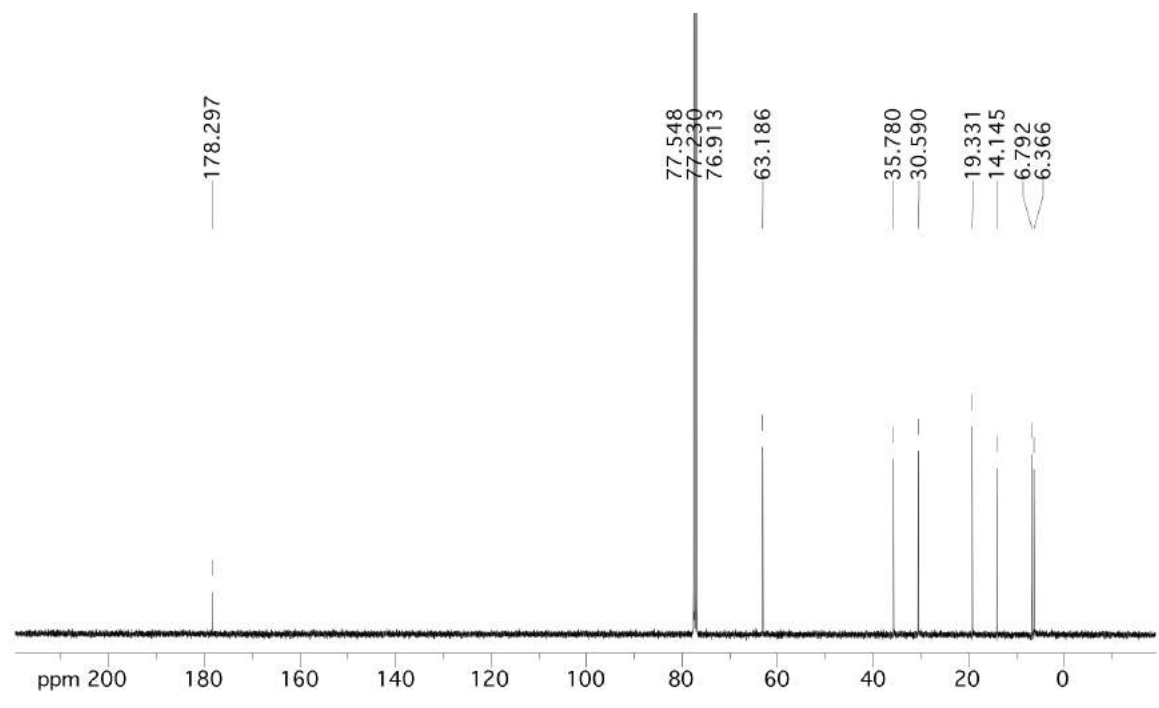
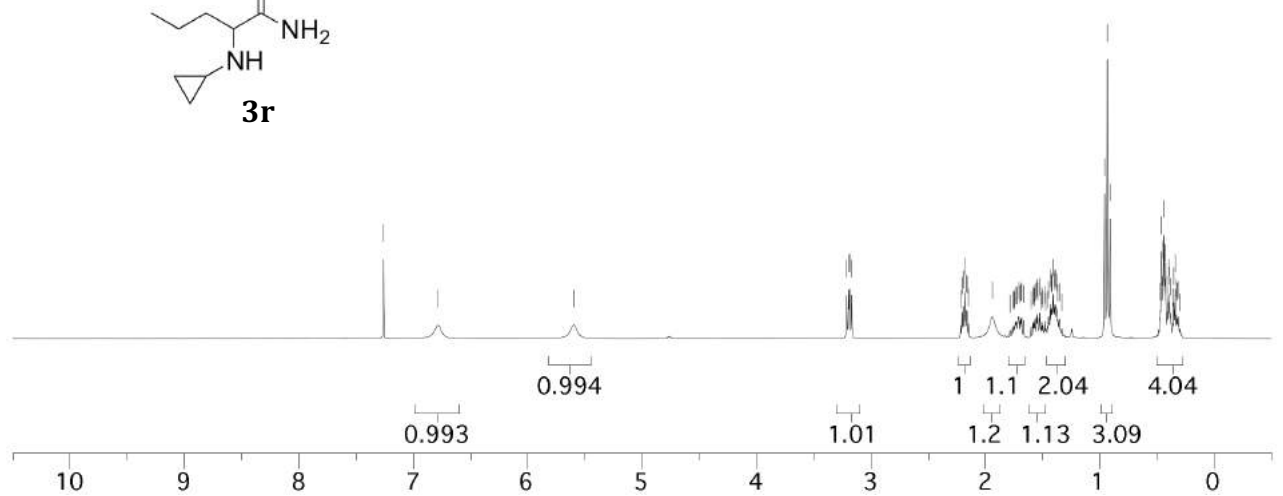
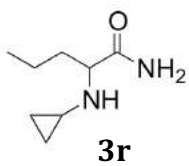


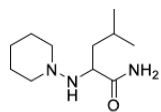




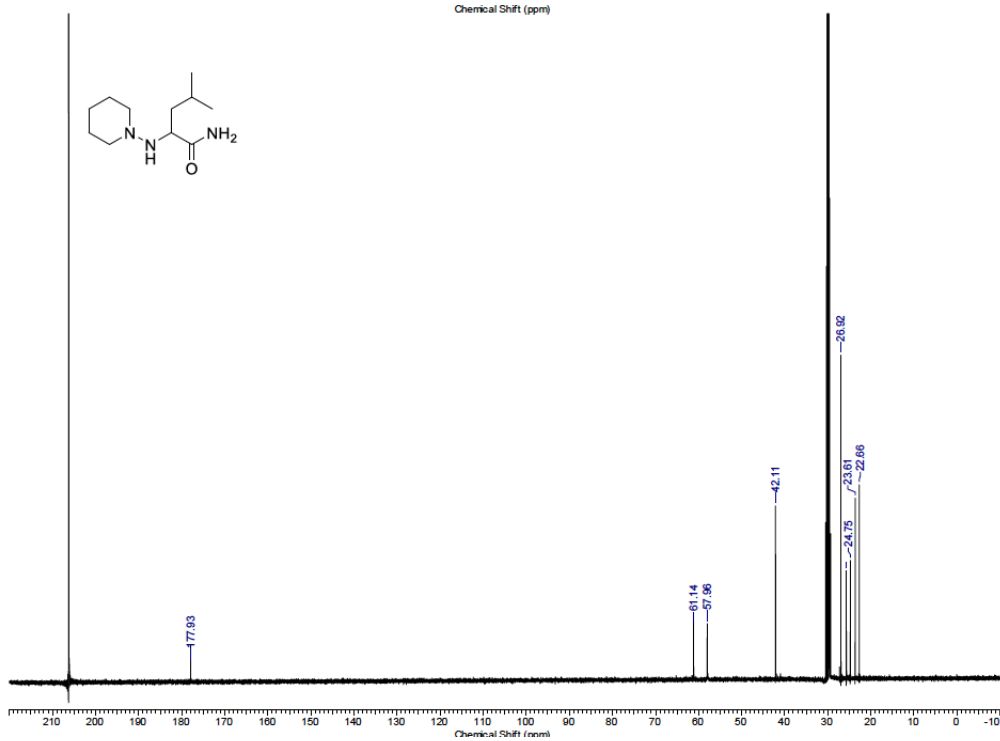
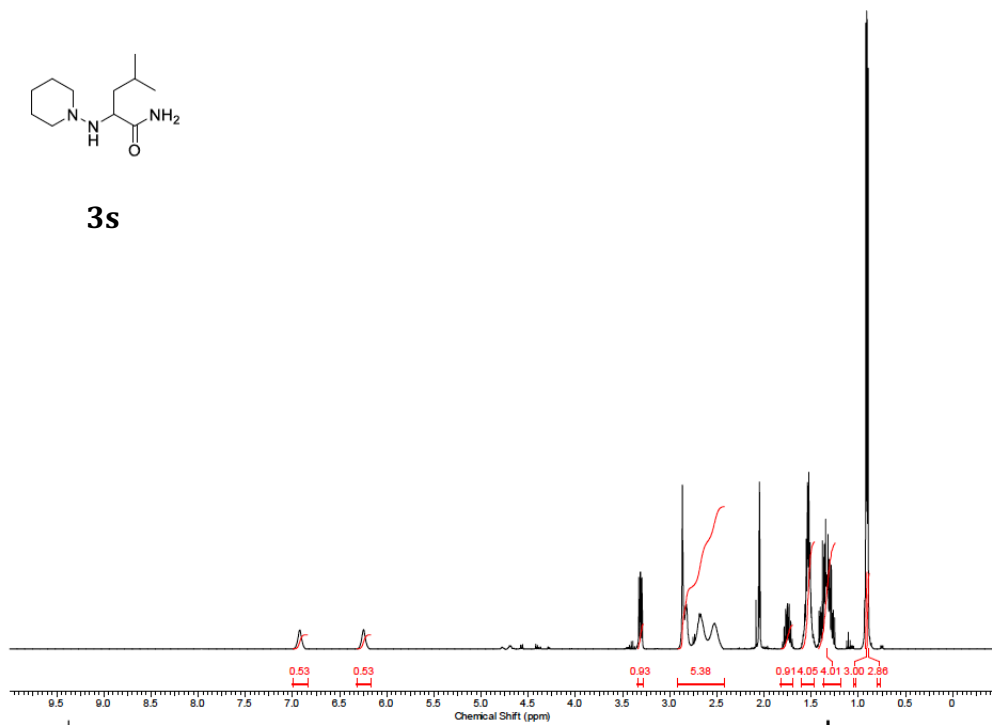


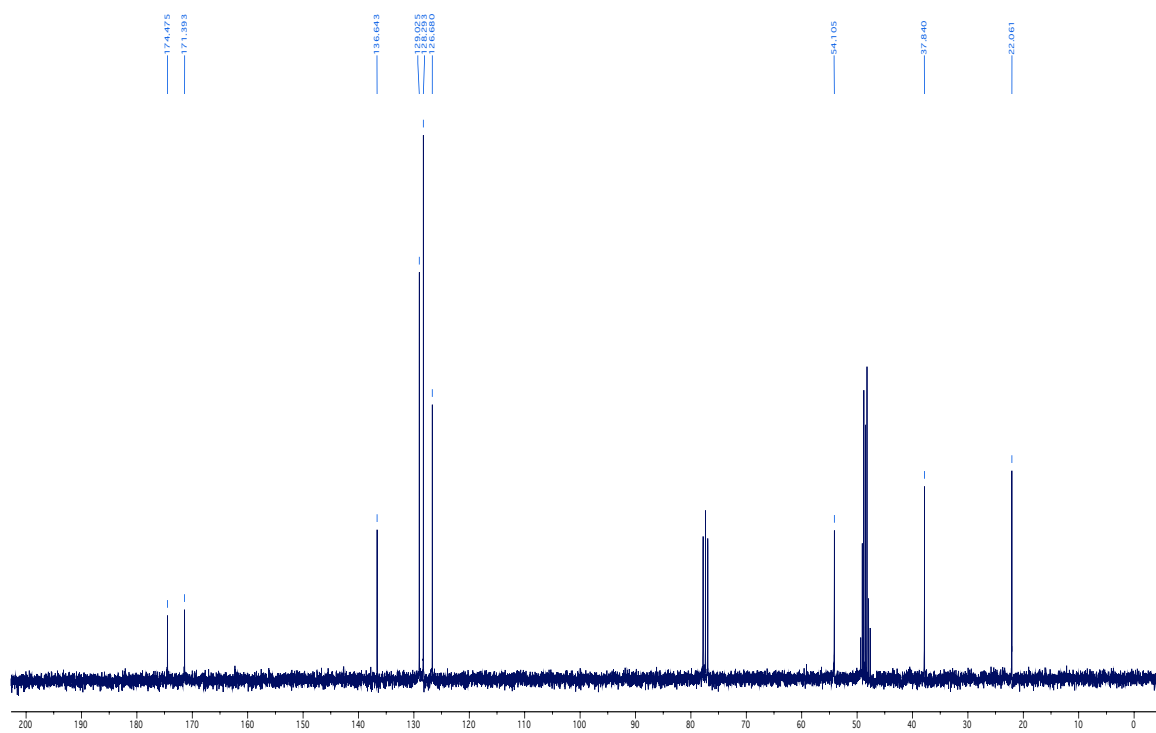
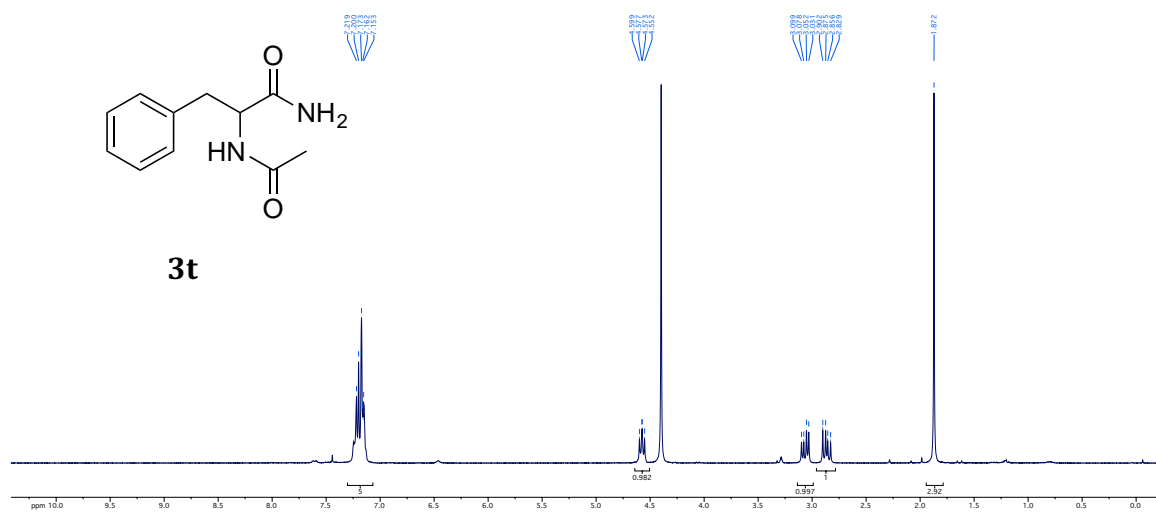
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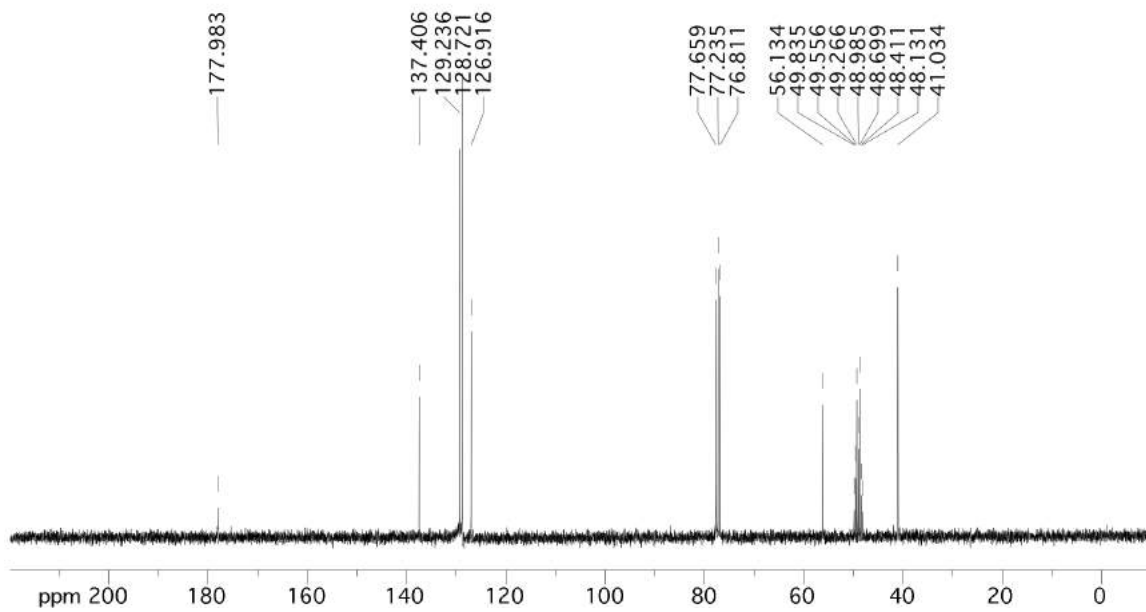
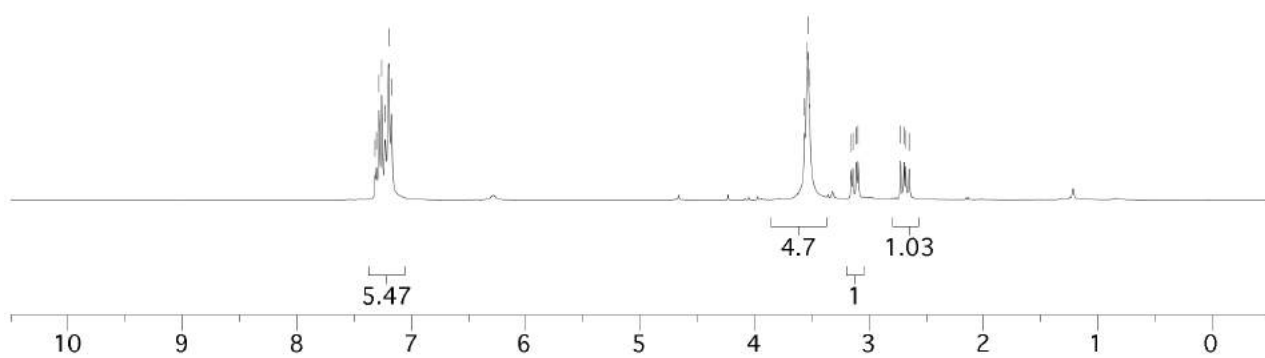
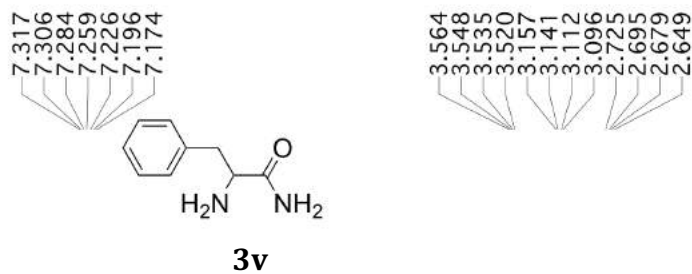


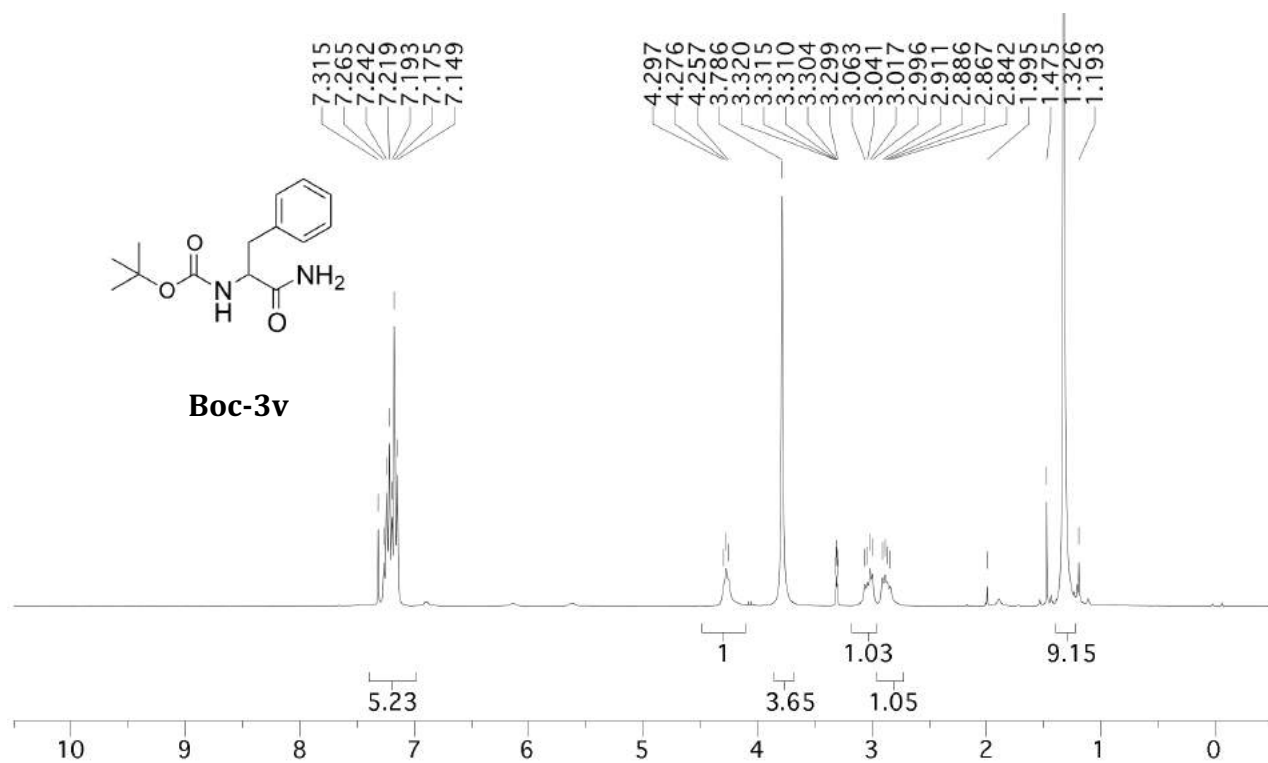


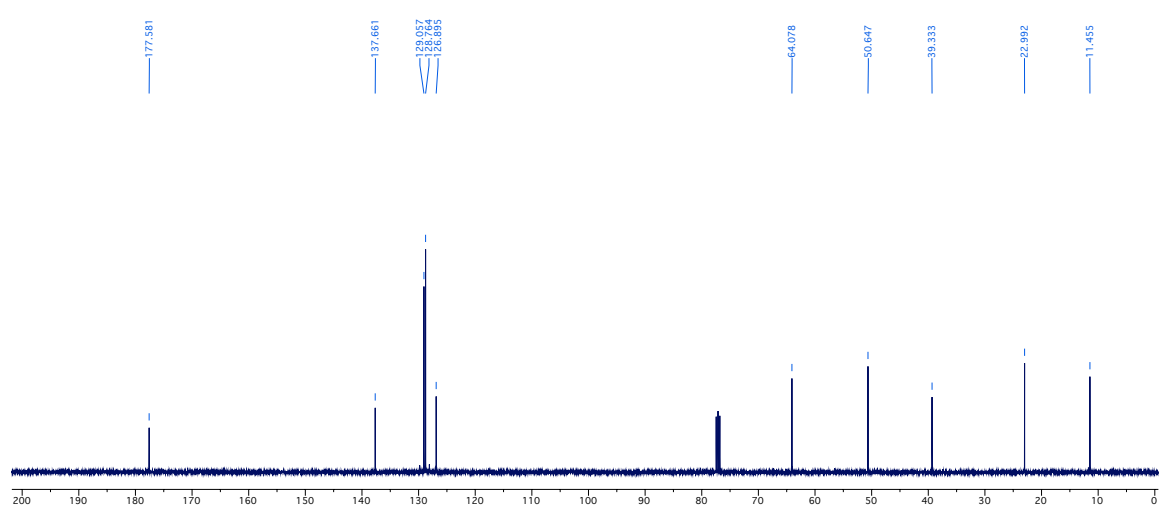
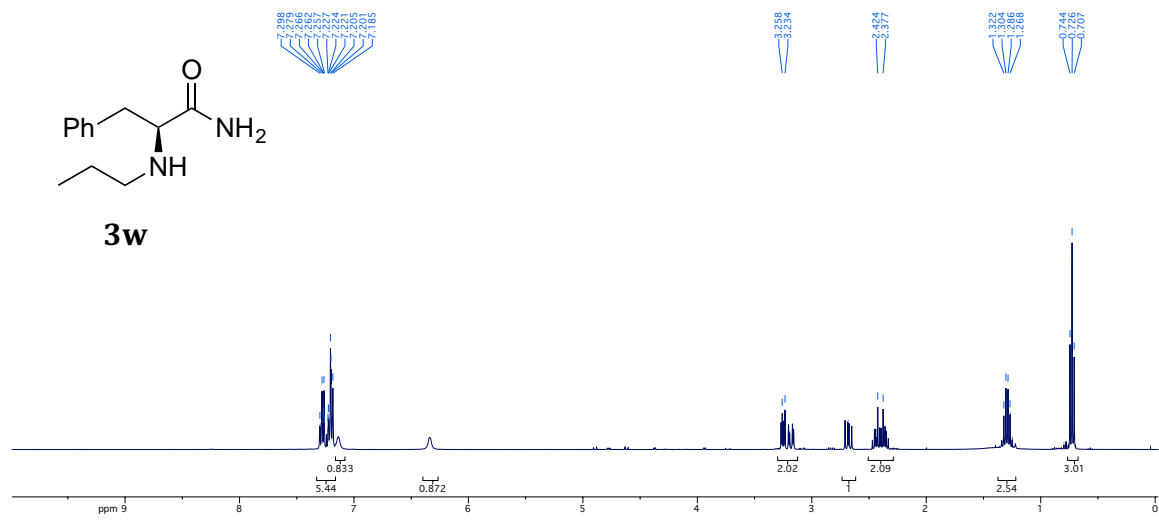
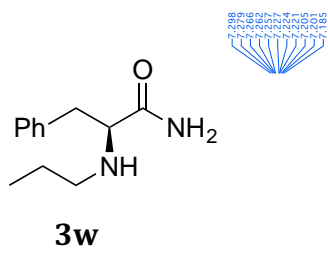
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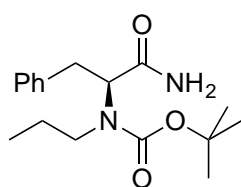












**Boc-3w**

